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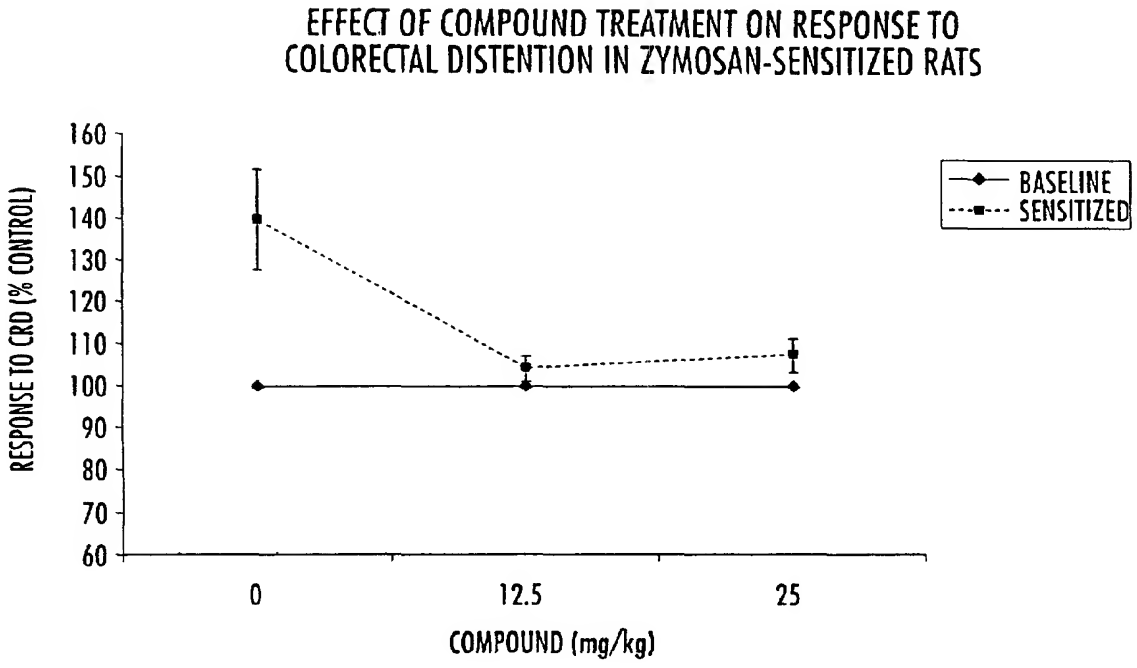
(54) Title: METHODS OF TREATING IRRITABLE BOWEL SYNDROME AND FUNCTIONAL DYSPEPSIA



(57) Abstract: The present invention relates to the use of certain glycol derivatives of xanthines for the treatment of irritable bowel syndrome and functional dyspepsia.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS OF TREATING IRRITABLE BOWEL SYNDROME AND FUNCTIONAL DYSPEPSIA

Background of the invention

The present invention relates to the use of certain glycol derivatives of xanthines, in medicine, particularly in the treatment and prophylaxis of irritable bowel syndrome and functional dispepsia.

Irritable bowel syndrome is a disease diagnosed positively by the presence of clinical features meeting the Rome criteria and by the exclusion of organic pathology justifying the symptoms. The Rome criteria for irritable bowel syndrome include continuous or recurrent symptoms of: abdominal pain or discomfort that is releived by defaecation; and/or associated with a change in frequency of stool; and/or associated with a change in consistency of stool; and two or more of the following: altered stool frequency, altered stool form, passage of mucus, and bloating or feeling of abdominal distention. IBS symptoms are reported in up to 22% of the population, with prevalence inwomen.

Certain pathophysiological mechanisms are known to lead to or aggravate irritable bowel syndrome, including abnormal motility, abnormal visceral perception, psychological distress and luminal factors irritating the small bowel or colon such as lactose, bile acids, short-chain fatty acids and food allergans.

IBS may present as diahrrea-predominant, constipation-predominant or alternating diahrrea and constipation forms.

Conventional treatments for IBS are directed toward treating the symptoms of the disease. Smooth muscle relaxant medications such as mebevarine have been employed. Alosetron, a 5HT3 antagonist, was recently approved for the treatment of diahrrea-predominant IBS.

Functional dyspepsia is a distinct type of dyspepsia. The term "dyspepsia" is defined as the general condition of indigestion and as such encompasses a variety of distinct dyspeptic conditions. There are several recognized types of dyspepsia, the most common being acid-related dyspepsia which is associated with excess gastric acidity and may lead to peptic ulcers, gastroesophageal reflux disease (GERD), and other conditions characterized by excess gastric acidity. Functional dyspepsia (FD), is not associated with excess gastric acidity. Rather, the primary pathophysiological causative factor for FD is unclear.

FD is a visceral hypersensitivity state characterized by chronic or recurrent upper abdominal symptoms in the absence of any identifiable organic pathology, such as peptic ulceration, gastric cancer, chronic pancreatitis or GERD. The absence of identifiable organic pathology is established using conventional techniques including endoscopy, radiography, histology, and other techniques known to those skilled in the art.

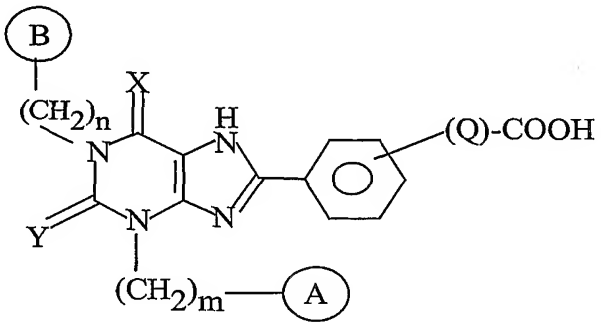
The primary symptoms of FD include upper abdominal pain or discomfort (often aggravated by food or milk or occurring after meals), early satiety (which can lead to weight loss or anorexia), nausea and vomiting, bloating, belching, and post-prandial fullness.

FD has been divided into subtypes based upon the predominant symptom(s) observed in the patient. "Ulcer-like" FD is characterized primarily by pain. "Reflux-like" FD is primarily characterized by heartburn that is often alleviated by acid-suppressing agents. It is believed that most cases of reflux-like FD can actually be attributed to GERD, and is not actually FD because the condition can be associated with an organic pathology. "Dysmotility-like" FD is characterized primarily by discomfort, bloating, nausea, vomiting, early satiety, and post-prandial fullness. "Unspecified" FD refers to FD patients having symptoms that do not fit into the above categories. Typically FD patients exhibit symptoms across the various sub-types.

The conventional treatment options for FD reflect the assumption that FD is attributable to the foregoing pathophysiological factors. The conventional treatment options for FD have proven to be of limited efficacy in many patients.

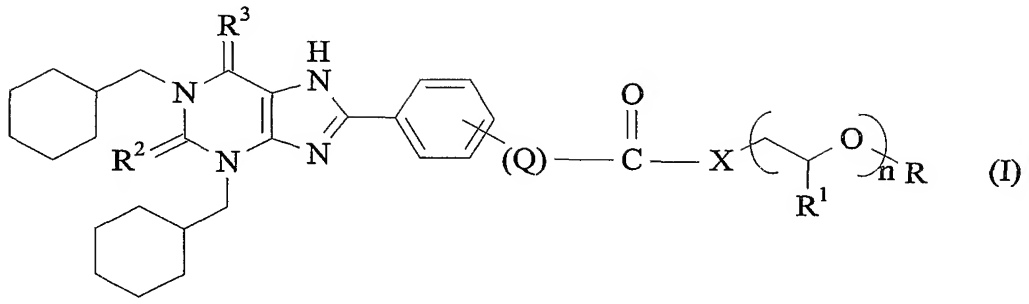
There remains a need for new methods for the treatment of IBS and FD.

PCT Publication No. WO 9604280 published 15 February 1996 to Glaxo Group Limited describes compounds of formula:



wherein m and n are independently integers from 0 to 10;
X and Y are independently oxygen or sulphur;
(-Q-) is $(-CH_2-)_p$ or $(-CH=CH-)_p$ where p is an integer of from 1 to 4; and
A and B are independently methyl, branched C_{3-6} alkyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;
and salts, solvates and pharmaceutically acceptable esters and amides thereof; and their use in treatment of inflammatory diseases, immune disorders, septic shock, circulatory disorders and gastrointestinal inflammation, infection or damage.

PCT Publication No. WO 98/35966, published 20 August 1998 to Glaxo Group Limited describes compounds of formula (I):



(I)

or a solvate thereof wherein:

X is -O- or -NH-;

Q is $(-CH_2-)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$ where p is an integer of from 0 to 4;

R^1 is hydrogen or methyl;

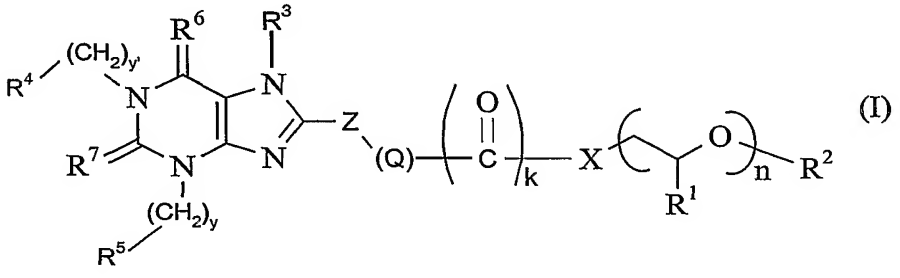
R^2 and R^3 independently represent O or S

n is an integer of 1 to 50; and

R is hydrogen or methyl;

and solvates and amides thereof; and their use in treatment of inflammatory conditions and immune disorders.

PCT Publication No. WO00/09507, published 24 February 2000 to Glaxo Group Limited describes compounds of formula (I) :



(I)

wherein

Z represents a 5 or 6 membered cycloalkyl, aryl, substituted cycloalkyl, or substituted aryl, said cycloalkyl, aryl, substituted cycloalkyl, or substituted aryl optionally containing one or more heteroatoms selected from O, N or S;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, C_{1-12}, alkyl, aryl, or aralkyl;

k represents 0 or 1

n represents an integer of 1 to 50;

X represents -O-, -N(H)-, -N(C_{1-6}alkyl)-, -N(C_{3-8}cycloalkyl)-, -N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), -N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-, $-CH_2O-$, $-CH_2NH-$, $-CH_2N(C_{1-6}alkyl)-$, $-CH_2N(C_{3-8}cycloalkyl)-$, or -$C_{1-12}$alkyl-.

m represents 0-12

Q represents $(-CH_2)_p$, (-CH=CH-)$_p$, (-C≡C-)$_p$, $(-(O)_{p1}CH2-)_p$ or $(-CH_2(O)_{p1})_p$ where

p and p^1 independently represent an integer of from 0 to 4;

y and y' independently represent integers from 0 to 10;

R^3 represents H, straight or branched C_{1-12}alkyl (optionally substituted by phenyl, -CO-phenyl, CN, -CO(C_{1-3}) alkyl, $-CO_2(C_{1-3})$alkyl, or containing one or more O atoms in the alkyl chain); C_{1-6} straight or branched alkenyl (optionally substituted by phenyl, -CO- phenyl, CN, -CO(C_{1-3}) alkyl, $-CO_2(C_{1-3})$alkyl, or containing one or more O atoms in the alkyl chain); C_{1-6} straight or branched alkynyl or a group -C_{1-3}alkyl $-NR^8R^9$

wherein R^8 and R^9 are independently H, C_{1-3}alkyl or together form a 5 or 6 membered heterocyclic group, optionally containing other heteroatoms selected from O, N or S;

R^4 and R^5 independently represent

-C_{3-8} cycloalkyl

-straight chain or branched C_{1-6}alkyl

-hydrogen

-straight or branched C_{2-6}alkenyl

-aryl or substituted aryl;

-heterocyclic group or subsituted heterocyclic group, including heteroaryl and substituted heteroaryl groups;

R^6 and R^7 independently represent O or S;

with the proviso that when

-y and y' both represent 1,

-k represents 1,

-p^1 represents zero,

-R^2 represents H or Me,

-R^3 represents H,

-X represents O or NH, and

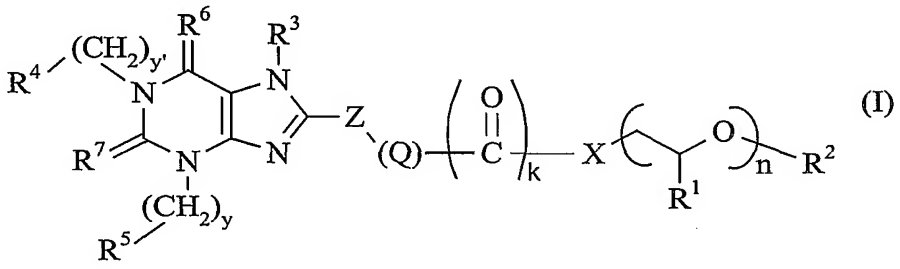
-Z represents phenyl

R^4 and R^5 do not both represent cyclohexyl;

and solvates thereof, and their use in treatment of inflammatory diseases, immune disorders, septic shock, circulatory disorders and gastrointestinal inflammation, infection or damage.

Brief Summary of the Invention

The present invention provides a method for the treatment or prophylaxis of irritable bowel syndrome in an animal, comprising administering a therapeutically effective amount of a compound of formula (I):



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), and

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O-)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof.

According to a second aspect, the present invention provides a method for the treatment or prophylaxis of functional dyspepsia in an animal. The method comprises administering to the animal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable solvate thereof.

According to a third aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable solvate thereof for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

According to another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable solvate thereof for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

According to another aspect, the present invention provides a method for the treatment or prophylaxis of irritable bowel syndrome in an animal comprising administering to the animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

According to another aspect, the present invention provides a method for the treatment or prophylaxis of functional dyspepsia in an animal comprising administering to the animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

According to another aspect, the present invention provides the use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

In yet another aspect, the present invention provides the use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

Brief Description of the Several Views of Drawings

Figure 1 is a graphical representation of the results of a study conducted in Zymosan-sensitized rats comparing the effect of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester (112.5 and 25 mg/kg) versus vehicle. Results are reported as response to colorectal distention (CRD) (as a percent of control) with increasing dosage of 0, 12.5, and 25 mg/kg of compound (sensitized --■--) as compared to baseline (--◆--).

Detailed Description of the Invention

As used herein, the term "aryl" refers to a carbocyclic group having 6-14 carbon atoms with at least one aromatic ring (e.g., phenyl or biphenyl) or multiple condensed rings in which at least one ring is aromatic, (e.g., 1, 2, 3, 4,-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl).

As used herein, the term "substituted aryl" refers to aryl as defined above optionally substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

As used herein, the term "aralkyl" refers to a C_{1-12}alkyl that may be a straight or a branched alkyl group that is substituted by an aryl or substituted aryl group.

As used herein, the term "heterocylic group" refers to a saturated or partially unsaturated, non-aromatic group having from 5 to 12 members in a single ring (e.g. imidazolidinyl, piperidyl, piperazinyl, pyrrolidinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl,

thiazylyl, thiadiazolyl, triazolyl or tetrazolyl) or multiple condensed rings (e.g. naphthpyridyl, quinoxalyl, indolizinyl or benzo[b]thienyl) and having 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S, within the ring. The heterocyclic group can optionally be unsubstituted or substituted (i.e., a "substituted heterocyclic group") with e.g. halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocyclic group, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

As used herein, the term "heteroaryl" refers to a heterocyclic group as defined above in which at least one ring is aromatic.

As used herein, the term "substituted heteroaryl" refers to a heterocyclic group optionally substituted with one or more substituents including halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "membered" in reference to any of cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic group, substituted heterocyclic group, heteroaryl and substituted heteroaryl refers to the total number of atoms (C, N, O and S) in the ring. Thus a 6-membered aryl is phenyl and a 6-membered heteroaryl is pyridine.

The term "alkyl" as used herein represents straight or branched hydrocarbon chains containing the indicated number of carbon atoms.

The term "alkenyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and one or more double bonds, for example propenylene.

The term "cycloalkyl" includes non-aromatic carbocyclic groups containing the specified number of carbon atoms and one or more double bonds, such as cyclopropane,

cyclobutane, cyclopentane, cyclohexane, cycloheptane and cyclooctane and includes bridged cycloalkyl groups, for example norbornyl.

As used herein, the terms "substituted alkyl" and "substituted cycloalkyl" refer to alkyl and cycloalkyl optionally substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "pharmaceutically acceptable solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Solvents, by way of example, include water, methanol, ethanol, or acetic acid.

In one particular aspect, the invention provides a compound of formula (I) wherein R^4 and R^5 are each independently selected from the group consisting of:
-C_{3-8}cycloalkyl;
-straight or branched C_{1-6}alkyl;
-H; and
-straight or branched C_{2-6}alkenyl.

In one embodiment, the compound of formula (I) is defined where R^4 and R^5 are each independently aryl or substituted aryl.

In another embodiment, the compound of formula (I) is defined where R^4 and R^5 are each independently selected from the group consisting of a heterocyclic group, substituted heterocyclic group, heteroaryl and substituted heteroaryl groups.

In another embodiment, the compound of formula (I) is defined where R^3 is H or C_{1-3}alkylNR^8R^9 and R^8 and R^9 are each independently H or C_{1-3}alkyl. In another embodiment, the compound of formula (I) is defined where R^3 is C_{1-3}alkylNR^8R^9 and R^8 and R^9 together with the N to which they are bonded form a 5 or 6 membered

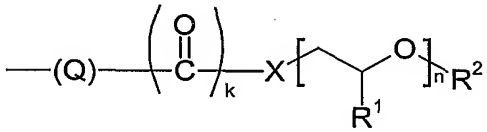
heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S.

In another embodiment, the compound of formula (I) is defined where Z is selected from the group consisting of a C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl and substituted C_6aryl.

In another embodiment, the compound of formula (I) is defined where Z is selected from the group consisting of a 5- or 6-membered heterocyclic group, substituted heterocyclic group, heteroaryl and substituted heteroaryl containing from one to three heteroatoms independently selected from O, N or S.

In one preferred embodiment, the compounds of formula (I) are defined where Z is a phenyl ring, thiophene ring or pyridine ring, more preferably phenyl.

The grouping



may be attached to Z in any suitable position. When Z is phenyl, preferably this group is attached to the phenyl ring in the para position.

In one preferred embodiment, the compounds of formula (I) are defined where R^1 is H or methyl.

In another preferred embodiment, the compounds of formula (I) are defined where R_2 is H, methyl or ethyl.

In one preferred embodiment, the compounds of formula (I) are defined where k is 1.

In one embodiment, the compounds of formula (I) are defined wherein n is 5-50. A preferred set of compounds of formula (I) are defined where n is from 8 to 20, more preferably from 8 to 15. However in certain embodiments of the present invention, such as wherein R^3 is other than H, n may preferably be shorter than 8 to 20, such as 5 to 20. Similarly, when k is 0, n may preferably be shorter than 8 to 20, such as 5-20.

Still another preferred set of compounds of formula (I) is defined where X is -O-, -N(H)-, -N(C_{1-6}alkyl)- or -N(C_{3-8}cycloalkyl)-. More preferably, X is -O-, -N(H)- or -N(CH_3)-.

In one preferred embodiment, the compounds of formula (I) are defined where Q is $(-CH_2-)_p$ or $(-CH=CH-)_p$. In one embodiment, p is 0-2, preferably 0-1. More preferably, compounds of formula (I) are defined where Q is $(-CH_2-)_p$ or $(-CH=CH-)_p$ and p is 0-4, more preferably 0-2.

One preferred set of compounds of formula (I) are defined where y and y' are the same. More preferably, compounds of formula I are defined where y and y' are both 1.

In another preferred embodiment, the compounds of formula I are defined where R_3 is methyl.

Another set of preferred compounds of formula (I) are defined where R^4 and R^5 are each independently selected from the group consisting of C_{1-6}alkyl, C_{3-8}cycloalkyl and aryl. More preferably, R^4 and R^5 are each independently selected from cyclobutyl, cyclopentyl, cyclohexyl, propyl, butyl, isopropyl, isobutyl, and phenyl. Although one preferred set of compounds is defined where R^4 and R^5 are different, another preferred set of compounds is defined where R^4 and R^5 are the same.

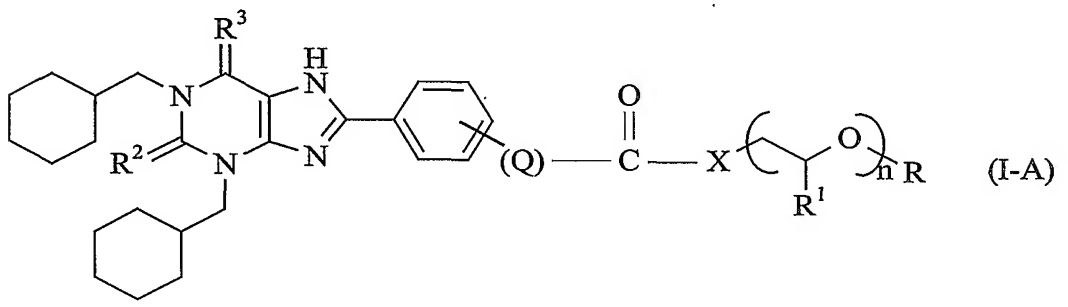
In another preferred embodiment, R^6 and R^7 are the same. More preferably, both R^6 and R^7 are 0.

According to a further aspect, the present invention provides a compound of formula (I) as defined above wherein X is -O- and R^1 is H; of these, compounds wherein n is an integer of 8 to 20 are preferred, and those wherein n is an integer of 8 to 15 are more preferred.

It is to be understood that the present invention includes all combinations and subsets of particular and preferred groups described hereinabove.

The invention also includes mixtures of compounds of formula (I) in any ratio wherein n varies.

In one embodiment, the present invention provides methods for the treatment or prophylaxis of gastrointestinal disorders, which methods comprise administering a therapeutically effective amount of a compound of formula (I-A):



(I-A)

wherein:

X is -O- or -NH-;

Q is $(-CH_2-)_p$, $(-CH=CH-)_p$ or $(-C\equiv C-)_p$ where p is 0 to 4;

R^1 is H or methyl;

R^2 and R^3 are each independently O or S;

n is an integer 1 to 50; and

R is H or methyl;

or a pharmaceutically acceptable solvate thereof.

Particularly preferred compounds for use in the methods of the invention include:

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopropylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-((1-propyl-3-benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2-thioxo-6-oxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-(3-cyanobenzyl))-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-methyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid-N-methyl-Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)phenyl] propionic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol Benzyl Ether Amide;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1,7-dimethyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine Heptaethylene Glycol Methyl Ether;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Nonaethylene Glycol Methyl Ether;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Pentaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

More particularly preferred compounds for use in the methods of the present invention include:

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid-N-methyl Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

In one preferred embodiment, the present invention provides methods for the treatment or prophylaxis of irritable bowel syndrome or functional dyspepsia which comprises admininstering a therapeutically effective amount of (E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester or a pharmaceutically acceptable solvate thereof.

The compounds of the present invention are capable of existing as geometric and optical isomers. All such isomers, individually and as mixtures, are included within the scope of the present invention. Where Q contains a double bond, compounds in the form of the E-geometric isomers are preferred.

Hereinafter reference to "compounds of formula (I)" shall include all compounds of formula (I), and specifically includes all compounds of formula (I-A), and pharmaceutically acceptable solvates thereof.

The compounds employed in the present invention are cell adhesion molecule inhibitors, and preferably endothelial cell adhesion molecule inhibitors. The term "cell adhesion molecule inhibitor" includes compounds which specifically block or inhibit proteins on the surface of animal cells that mediate cell-cell binding. Preferably, the term "cell adhesion molecule inhibitor" includes compounds which inhibit the expression of cell adhesion molecules.

The term "endothelial cell adhesion molecule inhibitor" includes compounds which specifically block or inhibit the adhesive interactions of leukocytes and the endothelium. These compounds can be identified by performing the endothelial cell adhesion assay as

decribed herein below. Preferably, the compounds have IC_{50} values in this assay of 500nM or less, more preferably 100nM or less and even more preferably 50nM or less. Preferably, the term "endothelial cell adhesion molecule inhibitor" includes compounds which inhibit the expression of endothelial cell adhesion molecules. More preferably, the endothelial cell adhesion molecules include ICAM-1 (Intercellular adhesion molecule-1), E-selectin, VCAM-1 and MadCAM.

The methods of the present invention involve treating or preventing irritable bowel syndrome, including diarrhea-predominant, constipation-predominant and alternating irritable bowel syndrome, and functional (non-ulcerative) dyspepsia by administering to an animal, a therapeutically effect amount of an endothelial cell adhesion molecule inhibitor, such as a compound of formula (I) or a solvate thereof. The methods of the present invention may be employed for the treatment or prophylaxis of irritable bowel syndrome and functional dyspepsia in animals generally, and particularly in mammals such as humans.

The term "therapeutically effective amount" refers to an amount of an endothelial cell adhesion molecule inhibitor, e.g., a compound of formula (I), which is effective for the treatment or prophylaxis of the stated condition. Thus, a therapeutically effective amount of a compound of formula (I) for the treatment or prophylaxis of irritable bowel syndrome or functional dyspepsia is an amount effective for the treatment or prophylaxis of irritable bowel syndrome or functional dyspepsia. The term "treatment" as used herein refers to the partial or total elimination of symptoms in an afflicted animal. The term "prophylaxis as used herein refers to the complete prevention of the condition in an animal as well as the reduction in severity and/or frequency of symptoms of the condition in an afflicted animal.

The amount of an endothelial cell adhesion molecule inhibitor, e.g., a compound of formula (I) or pharmaceutically acceptable solvate thereof, which is required to achieve the desired biological effect will depend on a number of factors such as the use for which it is intended, the means of administration, and the recipient, and will ultimately be in

the discretion of the attendent physician. A typical daily dose for the treatment of irritable bowel syndrome or functional dyspepsia, for instance, may be expected to lie in the range of 0.005 mg/kg - 100mg/kg, preferably 0.5-100 mg/kg, and most preferably 0.5-20 mg/kg. This dose may be administered as a single unit dose, as several separate unit doses or as a continuous infusion. An intravenous dose may be expected to lie in the range of 0.0025 mg/kg to 200 mg/kg and would typically be administered as an infusion.

According to the methods of the present invention, it is possible to administer the compounds of formula (I) neat, although it is preferred to administer the compounds of formula (I) in the form of a pharmaceutical formulation. Thus, in a further aspect of the present invention, there are provided pharmaceutical compositions comprising, as active ingredient, a compound of formula (I) or a pharmaceutically acceptable solvate thereof, together with at least one pharmaceutically acceptable carrier or excipient. These pharmaceutical compositions may be used in the prophylaxis or treatment of irritable bowel syndrome and functional dyspepsia. The carrier must be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or liquid and the formulation is preferably formulated as a unit dose formulation, for example, a tablet which may contain from 0.05 to 95% by weight of the active ingredients. If desired other physiologically active ingredients may also be incorporated in the pharmaceutical compositions of the invention. In one embodiment, the methods of the present invention comprise administering a therapeutically effective amount of a combination of a compound of formula (I) or a pharmaceutically acceptable solvate thereof and alosetron or a pharmaceutically acceptable salt thereof.

Possible formulations include those suitable for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular, or intravenous), rectal, topical including transdermal, intranasal and inhalation administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the condition being treated and on the nature of the active compound.

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, lozenges, each containing a predetermined amount of the

active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically a flavoured base, such as sugar and acacia or tragacanth and pastilles comprising the active compound in an inert base, such as gelatine and glycerine or sucrose acacia.

Formulations suitable for parenteral administration typically comprise sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Additional formulations suitable for parenteral administration include formulations containing physiologically suitable co-solvents and/or complexing agents such as surfactants and cyclodextrins. Oil-in-water emulsions are also suitable formulations for parenteral formulations. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

Formulations suitable for rectal administration are preferably provided as unit-dose suppositories comprising the active ingredient in one or more solid carriers forming the suppository base, for example, cocoa butter.

Formulations suitable for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethyleneglycols, alcohols, and combinations thereof. The active ingredient is typically present in such formulations at a concentration of from 0.1 to 15% w/w.

Formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the active compound with liquids or finely divided solid carriers or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape.

For example a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of powdered active ingredient and inert liquid diluent.

Suitable formulations for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers, or insufflators.

Therefore, according to a further aspect of the present invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable solvate thereof in the preparation of a medicament for the prophylaxis or treatment of irritable bowel syndrome or functional dyspepsia.

Compounds of formula (I) may be prepared and formulated as described in PCT application publication Nos. WO 98.35966 and WO 00.09507, the subject matter of which is incorporated herein by reference in their entirety.

The invention will now be described by way of illustration only, by the following examples:

Cell Adhesion Assay

The antiadhesion activity of compounds described herein was determined using a modification of the previously described method, Jurgensen, C.H. et. al., *J. Immunol.* 1990, 144: 653-661. The adhesiveness of cytokine-stimulated human umbilical vein endothelial cells was assessed by quantitating the adherence of fluorescently-labelled (calcein-AM, Molecular Probes, Eugene, OR) leukocytes to endothelial cell monolayers. Activity was determined by calculating inhibition of cytokine-stimulated adhesion minus the basal adhesion (unstimulated).

Rodent Model of Zymosan-Induced Hyperalgesia

Protocol for Evaluation of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester in a Rodent Model of Zymosan-Induced Hyperalgesia

Animals

Adult male Sprague-Dawley rats (400-425 g) housed 1-2 per cage in the animal care facility at the University of Iowa (approved by the American Association for Accreditation of Laboratory Animal Care). All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Iowa.

Surgical Preparation

Rats were deeply anesthetized with pentobarbital sodium (45 mg/kg) administered intraperitoneally. Electrodes were stitched into the external oblique musculature for electromyographic (EMG) recording. Electrode leads were tunneled subcutaneously and exteriorized at the nape of the neck for future access. After surgery, rats were housed separately and allowed to recuperate for at least 3 days prior to testing.

Behavioral Testing

The descending colon and rectum were distended by pressure-controlled inflation of a 7-8-cm-long flexible latex balloon tied around a flexible tube. The balloon was lubricated , inserted into the colon via the anus, and anchored by taping the balloon catheter to the base of the tail. Noxious phasic colorectal distension (CRD, 80 mm Hg, 20 seconds) was achieved by opening a solenoid gate to a constant pressure air reservoir. Intracolonic pressure was continuously monitored by the aid of a pressure control device. Response was quantified as the visceromotor response (VMR), a contraction of the abdominal and hindlimb musculature. EMG activity produced by contraction of the external oblique musculature was quantified using Spike2 software (Cambridge Electronic Designs). Each distension trial lasted 60 seconds, and EMG activity was quantitated in 1-second bins for 20 seconds before distension (baseline), during distention, and 20 seconds after

distention. The increase in total number of recorded counts during distention is defined as the response.

Compound Testing

Stable baseline responses to CRD (80 mm Hg, 20 seconds, 4 minutes apart) was obtained in conscious, unsedated rats before any treatment, followed by oral gavage with 2 doses of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester (12.5 mg/kg and 25 mg/kg) (Time 0). Control animals received vehicle only. At time 16 hours, a pre-zymosan response to distention was measured, followed by second oral doses of experimental compound. The animals were then briefly anesthetized with halothane, and zymosan (1 mL, 25 mg/mL) was instilled into the colon with a gavage needle inserted to a depth of about 7-8 cm, to produce inflammation and enhance the VMR to CRD. Four hours after intracolonic treatment, responses to CRD were quantified as described above.

Results Discussion

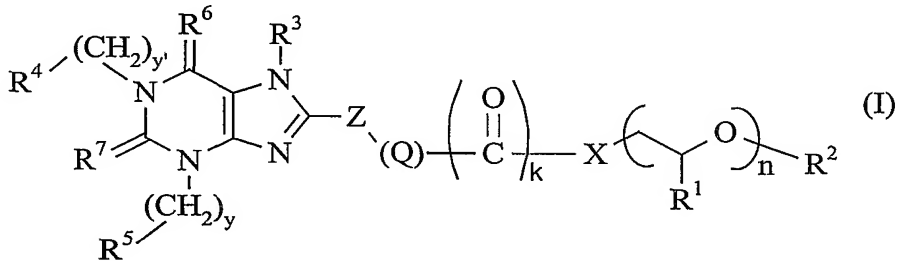
Hyperalgesia is an altered sensory state of increased sensitivity to pain. Visceral hyperalgesia associated with the gastrointestinal tract may arise secondary to infection or inflammation. Such altered visceral sensation, as exemplified by increased sensitivity to colorectal distention, has been observed in patients with functional bowel disorders. Coutinho, Meller, and Gebhart have shown that intracolonic instillation of zymosan, a yeast cell wall derivative which acts as an inflamogen, produces colonic inflammation and enhanced visceromotor responses to colorectal distention as a measurement of response to pain (Ref: Coutinho SV, Meller ST, Gebhart GF. Intracolonic zymosan produces visceral hyperalgesia in the rat that is mediated by spinal NMDA and non-NMDA receptors. Brain Res 1996; 736:7-15).

The results of the study are reported in **Figure 1**. Results from evaluation of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester in this model show that this compound was

efficacious in decreasing zymosan-induced visceral hypersensitivity to colorectal distention. Both doses (12.5 and 25 mg/kg) of the compound effectively decreased the response to colorectal distention down to baseline levels. Results are expressed as percentage of control, with baseline levels at 100% of control. Increased hypersensitivity is evidenced by increases over 100% of responses to colorectal distention. Overall, these data indicate that (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester is useful for the treatment and prophylaxis of irritable bowel syndrome and functional dyspepsia.

Claims

1. A method for the treatment or prophylaxis of irritable bowel syndrome in an animal, said method comprising administering to said animal a therapeutically effective amount of a compound of formula (I):



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), and

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O-)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

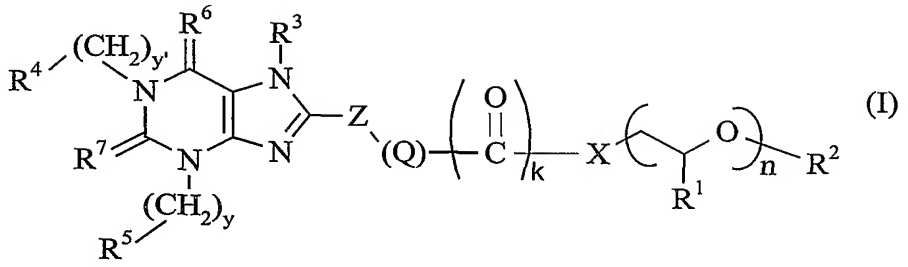
-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof.

2. A method for the treatment or prophylaxis of functional dyspepsia in an animal, said method comprising administering to said animal a therapeutically effective amount of a compound of formula (I):



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

$-N(C_{1-6}alkyl)-$,

$-N(C_{3-8}cycloalkyl)-$,

$-N(C_{1-8}alkyl)(C_{3-8}$ cycloalkyl), and

$-N[(CH_2CH_2O)_m(C_{1-12}$ alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl,

CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof.

3. The method according to claim 1 or 2 wherein the compound of formula (I) is selected from the group consisting of:

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopropylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-((1-propyl-3-benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2-thioxo-6-oxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-(3-cyanobenzyl))-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-methyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid-N-methyl-Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)phenyl] propionic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol Benzyl Ether Amide;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1,7-dimethyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine Heptaethylene Glycol Methyl Ether;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Nonaethylene Glycol Methyl Ether;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Pentaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

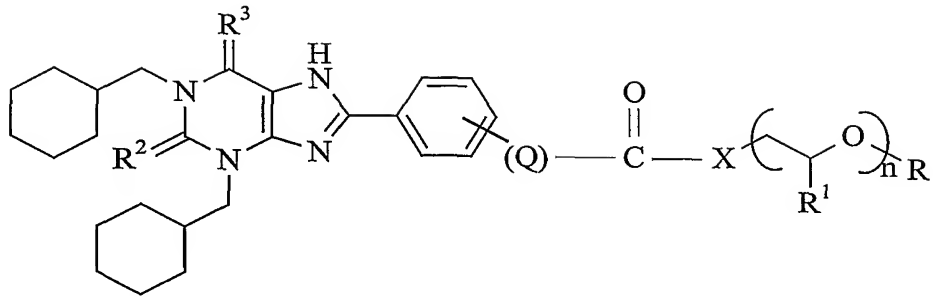
(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

4. The method according to claim 1 or 2, wherein the compound of formula (I) is (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester, or a pharmaceutically acceptable solvate thereof.

5. The method according to claim 1 or 2, wherein the compound of formula (I) is a compound of formula (I-A):



(I-A)

wherein:

X is -O- or -NH-;

Q is selected from the group consisting of $(-CH_2-)_p$, $(-CH=CH-)_p$ and $(-C\equiv C-)_p$ where p is 0 to 4;

R^1 is H or methyl;

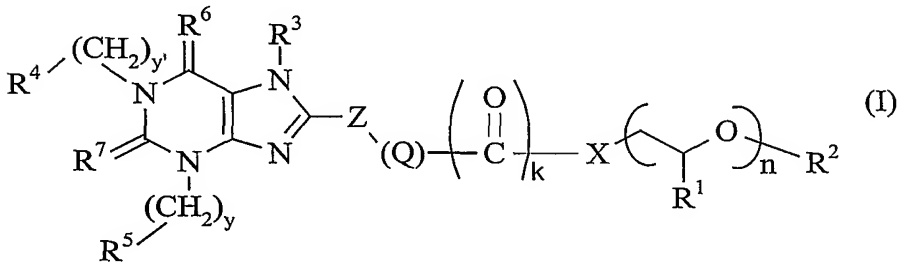
R^2 and R^3 are each independently O or S.

n is an integer 1 to 50; and

R is H or methyl;

or a pharmaceutically acceptable solvate thereof.

6. The use of a compound of formula (I) :



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), and

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

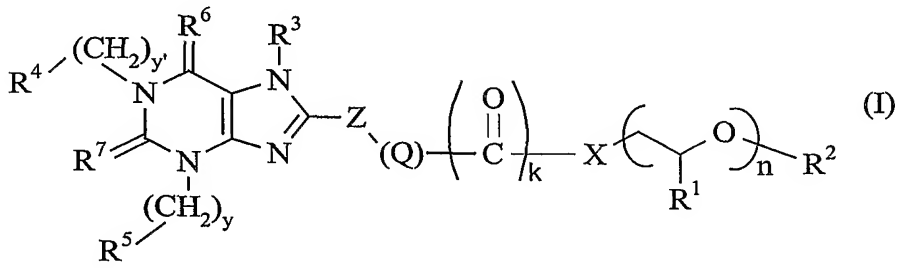
-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof, for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

7. The use of a compound of formula (I) :



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl),

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-,

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O-)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl-NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

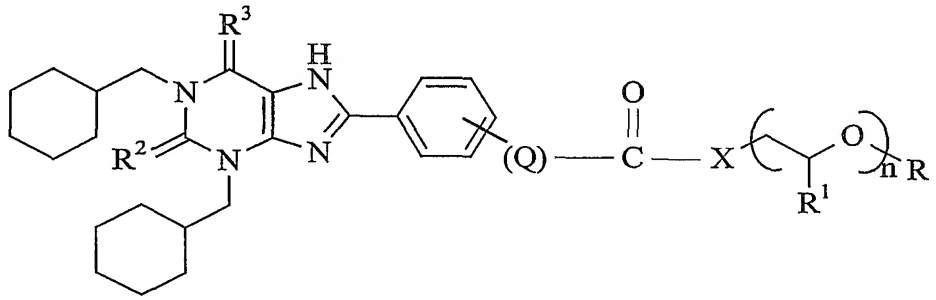
-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof, for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

8. The use according to claim 6 or 7, wherein the compound of formula (I) is a compound of formula (I-A)



(I-A)

wherein:

X is -O- or -NH-;

Q is selected from the group consisting of $(-CH_2-)_p$, $(-CH=CH-)_p$ and $(-C\equiv C-)_p$ where p is 0 to 4;

R^1 is H or methyl;

R^2 and R^3 are each independently O or S;

n is an integer 1 to 50; and

R is H or methyl;

or a pharmaceutically acceptable solvate thereof.

9. The use according to claim 6 or 7 wherein the compound of formula (I) is selected from the group consisting of:

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopropylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-((1-propyl-3-benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2-thioxo-6-oxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-(3-cyanobenzyl))-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-methyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid-N-methyl-Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)phenyl] propionic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol Benzyl Ether Amide;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1,7-dimethyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine Heptaethylene Glycol Methyl Ether;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Nonaethylene Glycol Methyl Ether;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Pentaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

10. The use according to any of claims 6, 7 and 8 wherein the compound of formula (I) is (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester or a pharmaceutically acceptable solvate thereof.

11. A method for the treatment or prophylaxis of irritable bowel syndrome in an animal, said method comprising administering to said animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

12. A method for the treatment or prophylaxis of functional dyspepsia in an animal, said method comprising administering to said animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

13. The use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

14. The use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

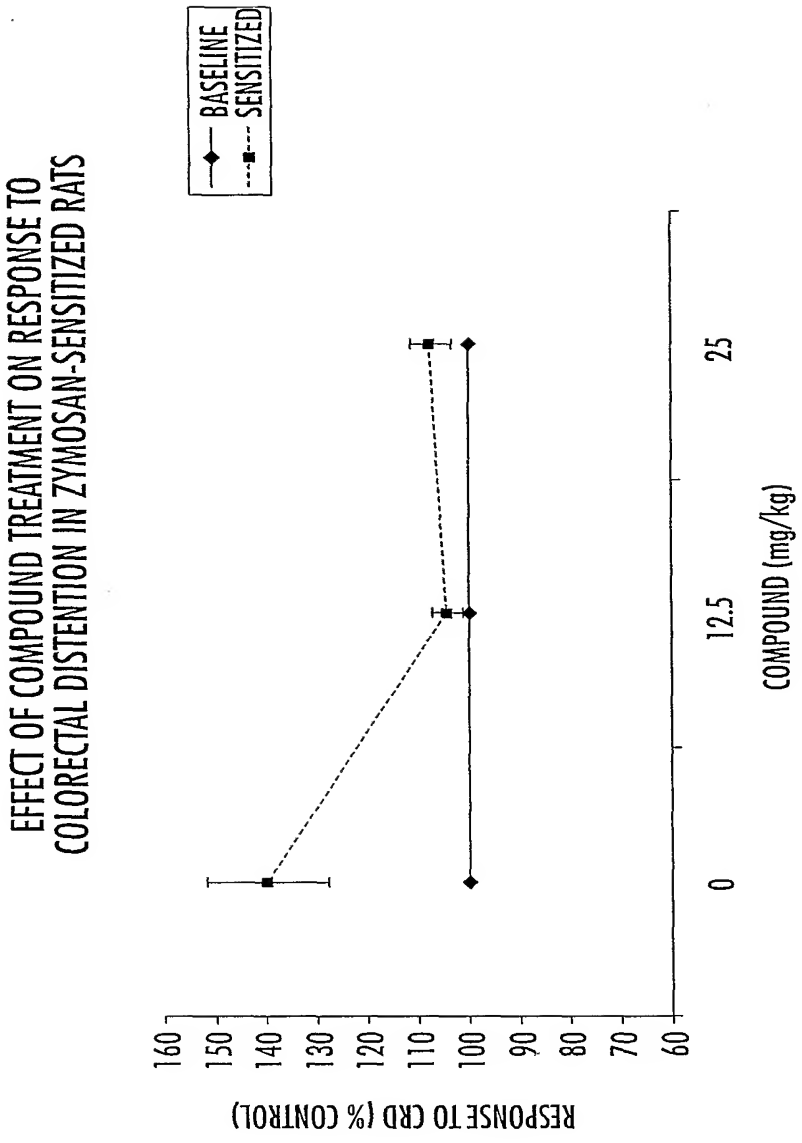

EFFECT OF COMPOUND TREATMENT ON RESPONSE TO COLORECTAL DISTENTION IN ZYMOSAN-SENSITIZED RATS
BASELINE
SENSITIZED
RESPONSE TO CRD (% CONTROL)
160
150
140
130
120
110
100
90
80
70
60
0
12.5
25
COMPOUND (mg/kg)

FIG. 1.

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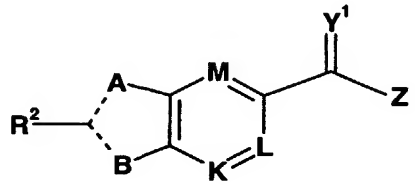
(54) Title: VIRAL POLYMERASE INHIBITORS



(I)

(57) Abstract: An isomer, enantiomer, diastereoisomer, or tautomer of a compound, represented by formula (I):wherein:A is O, S, NR^1, or CR_1, wherein R_1 is defined herein; represents either a single or a double bond;R_2 is selected from: H, halogen, R_{21}, OR_{21}, SR_{21}, $COOR_{21}$, $SO_2N(R^{22})_2$, $N(R^{22})_2$, , $CON(R^{22})_2$, $NR^{22}C(O)R^{22}$ or $NR^{22}C(O)NR^{22}$ wherein R^{21} and each R^{22} is defined herein;B is NR^3 or CR^3, with the proviso that one of A or B is either CR^1 or CR^3, wherein R^3 is defined herein;K is N or CR^4, wherein R^4 is defined herein;L is N or CR^5, wherein R^5 has the same definition as R^4 defined above;M is N or CR^7, wherein R^7 has the same definition as R^4 defined above;Y^1 is O or S;Z is $N(R^{6a})R^6$ or OR^6, wherein R^{6a} is H or alkyl or $NR^{61}R^{62}$ wherein R^{61} and R^{62} are defined herein;a salt or a derivative thereof, as an inhibitor of HCV NS^{5B} polymerase.

VIRAL POLYMERASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The invention relates to inhibitors of RNA dependent RNA polymerases, particularly those viral polymerases within the Flaviviridae family, more particularly to HCV polymerase.

BACKGROUND OF THE INVENTION

About 30,000 new cases of hepatitis C virus (HCV) infection are estimated to occur in the United States each year (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051). HCV is not easily cleared by the hosts' immunological defences; as many as 85% of the people infected with HCV become chronically infected. Many of these persistent infections result in chronic liver disease, including cirrhosis and hepatocellular carcinoma (Hoofnagle, J.H.; 1997; *Hepatology* **26**: 15S-20S). There are an estimated 170 million HCV carriers world-wide, and HCV-associated end-stage liver disease is now the leading cause of liver transplantation. In the United States alone, hepatitis C is responsible for 8,000 to 10,000 deaths annually. Without effective intervention, the number is expected to triple in the next 10 to 20 years. There is no vaccine to prevent HCV infection. Prolonged treatment of chronically infected patients with interferon or interferon and ribavirin is the only currently approved therapy, but it achieves a sustained response in fewer than 50% of cases (Lindsay, K.L.; 1997; *Hepatology* **26**: 71S-77S, and Reichard, O.; Schvarcz, R.; Weiland, O.; 1997 *Hepatology* **26**: 108S-111S).

HCV belongs to the family *Flaviviridae*, genus *hepacivirus*, which comprises three genera of small enveloped positive-strand RNA viruses (Rice, C.M.; 1996; "*Flaviviridae*: the viruses and their replication"; pp. 931-960 in *Fields Virology*; Fields, B.N.; Knipe, D.M.; Howley, P.M. (eds.); Lippincott-Raven Publishers, Philadelphia Pa.). The 9.6 kb genome of HCV consists of a long open reading frame (ORF) flanked by 5' and 3' non-translated regions (NTR's). The HCV 5' NTR is 341 nucleotides in length and functions as an internal ribosome entry site for cap-independent translation initiation (Lemon, S.H.; Honda, M.; 1997; *Semin. Virol.* **8**: 274-288). The HCV polyprotein is cleaved co- and post-translationally into at least 10 individual polypeptides (Reed, K.E.; Rice, C.M.; 1999; *Curr. Top.*

Microbiol. Immunol. **242**: 55-84). The structural proteins result from signal peptidases in the N-terminal portion of the polyprotein. Two viral proteases mediate downstream cleavages to produce non-structural (NS) proteins that function as components of the HCV RNA replicase. The NS2-3 protease spans the C-terminal half of the NS2 and the N-terminal one-third of NS3 and catalyses *cis* cleavage of the NS2/3 site. The same portion of NS3 also encodes the catalytic domain of the NS3-4A serine protease that cleaves at four downstream sites. The C-terminal two-thirds of NS3 is highly conserved amongst HCV isolates, with RNA-binding, RNA-stimulated NTPase, and RNA unwinding activities. Although NS4B and the NS5A phosphoprotein are also likely components of the replicase, their specific roles are unknown. The C-terminal polyprotein cleavage product, NS5B, is the elongation subunit of the HCV replicase possessing RNA-dependent RNA polymerase (RdRp) activity (Behrens, S.E.; Tomei, L.; DeFrancesco, R.; 1996; *EMBO J.* **15**: 12-22; and Lohmann, V.; Körner, F.; Herian, U.; Bartenschlager, R.; 1997; *J. Virol.* **71**: 8416-8428). It has been recently demonstrated that mutations destroying NS5B activity abolish infectivity of RNA in a chimp model (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051).

The development of new and specific anti-HCV treatments is a high priority, and virus-specific functions essential for replication are the most attractive targets for drug development. The absence of RNA dependent RNA polymerases in mammals, and the fact that this enzyme appears to be essential to viral replication, would suggest that the NS5B polymerase is an ideal target for anti-HCV therapeutics.

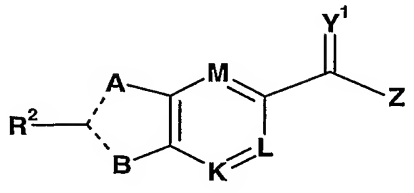
WO 00/06529 reports inhibitors of NS5B which are α, γ-diketoacids.
WO 00/13708, WO 00/10573, WO 00/18231, and WO 01/47883 report inhibitors of NS5B proposed for treatment of HCV.

SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a novel series of compounds having improved inhibitory activity against HCV polymerase.

In a first aspect of the invention, there is provided an isomer, enantiomer,

diastereoisomer, or tautomer of a compound, represented by formula I:



(I)

wherein:

A is O, S, NR^1, or CR^1, wherein R^1 is selected from the group consisting of: H, (C_{1-6})alkyl optionally substituted with:

-halogen, OR^{11}, SR^{11} or $N(R^{12})_2$, wherein R^{11} and each R^{12} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, said aryl or **Het** optionally substituted with R^{10}; or

both R^{12} are covalently bonded together and to the nitrogen to which they are both attached to form a 5, 6 or 7-membered saturated heterocycle;

----- represents either a single or a double bond;

R^2 is selected from: H, halogen, R^{21}, OR^{21}, SR^{21}, $COOR^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})_2$, , $CON(R^{22})_2$, $NR^{22}C(O)R^{22}$ or $NR^{22}C(O)NR^{22}$ wherein R^{21} and each R^{22} is independently H, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, said R^{21} and R^{22} being optionally substituted with R^{20}, or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached; wherein R^{10} and R^{20} is each:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{3-6})cycloalkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-}$

$_{6}$alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

j) $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$; wherein $\mathbf{R^{150}}$ is defined as:

- 1 to 3 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-}

$_6$)alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently

bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$, or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or $O(C_{1-6}$alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$,

SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

B is NR^3 or CR^3, with the proviso that one of **A** or **B** is either CR^1 or CR^3, wherein R^3 is selected from (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**,

said alkyl, cycloalkyl, bicycloalkyl, aryl, **Het**, alkyl-aryl and alkyl-**Het** being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C_{1-6})alkyl optionally substituted with:

- OR^{31} or SR^{31} wherein R^{31} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or
- $N(R^{32})_2$ wherein each R^{32} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{32} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) OR^{33} wherein R^{33} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

c) SR^{34} wherein R^{34} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; and

d) $N(R^{35})_2$ wherein each R^{35} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{35} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-

membered saturated heterocycle;

K is N or CR^4, wherein R^4 is H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^4 is OR^{41} or SR^{41}, COR^{41} or $NR^{41}COR^{41}$ wherein each R^{41} is independently H, (C_{1-6})alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or R^4 is $NR^{42}R^{43}$ wherein R^{42} and R^{43} are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or both R^{42} and R^{43} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

L is N or CR^5, wherein R^5 has the same definition as R^4 defined above;

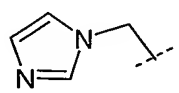
M is N or CR^7, wherein R^7 has the same definition as R^4 defined above;

Y^1 is O or S;

Z is OR^6, wherein R^6 is H, (C_{1-6})alkyl being optionally substituted with: halo, hydroxy, carboxy, amino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, and C_{1-6} alkylamino; or R^6 is C_{1-6} alkylaryl optionally substituted with: halogen, cyano, nitro, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}alkanoyl, $-(CH_2)_{1-6}-COOR^7$, $-(CH_2)_{1-6}-CONR^7R^8$, $-(CH_2)_{1-6}-NR^7R^8$, $-(CH_2)_{1-6}-NR^7COR^8$, $-(CH_2)_{1-6}-NHSO_2R^7$, $-(CH_2)_{1-6}-OR^7$, $-(CH_2)_{1-6}-SR^7$, $-(CH_2)_{1-6}-SO_2R^7$, and $-(CH_2)_{1-6}-SO_2NR^7R^8$, wherein each R^7 and each R^8 is H or C_{1-6} alkyl,

or **Z** is NR^9R^{10} wherein each of R^9 and R^{10} is selected from: H, C_{1-6}alkoxy, or C_{1-6}alkyl optionally substituted with halo, hydroxy, carboxy, amino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, and C_{1-6} alkylamino;

or a salt thereof;

with the proviso that when **A** is CR^1, R^1 is Me, R^2 is pyridine or 

, **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not H;

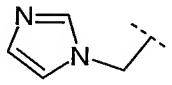
and with the proviso that when **A** is NR^1, R^1 is H, R^2 is phenyl, **B** is CR^3, R^3 is

phenyl, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not H;

and with the proviso that when **A** is S, R^2 is bromine, **B** is CR^3, R^3 is Me, **K** is CH, **L** is CH, **M** is CR^7, R^7 is H or Me, Y^1 is O, and **Z** is OR^6, then R^6 is not H;

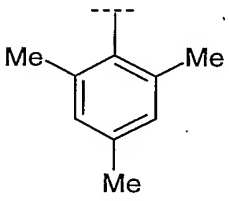
and with the proviso that when **A** is O, R^2 is H, **B** is CR^3, R^3 is phenyl, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not H;

and with the proviso that when **A** is CR^1, R^1 is Me, R^2 is pyridine, **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Me;

and with the further proviso that when **A** is CR^1, R^1 is Me, R^2 is  , **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Et;

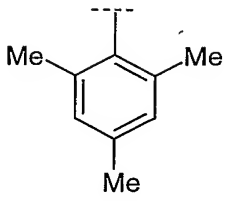
and with the further proviso that when **A** is CR^1, R^1 is CH, R^2 is Me, **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Et;

and with the further proviso that when **A** is CR^1, R^1 is Et, R^2 is Me, **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not $CH_2CH_2N(Me)_2$;

and with the further proviso that when **A** is CH, R^2 is Me, **B** is NR^3, R^3 is 

, **K** is N, **L** is CR^5, R^5 is Me, **M** is CR^7, R^7 is OH, Y^1 is O, and **Z** is OR^6 then R^6 is not Et;

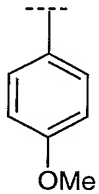
and with the further proviso that when **A** is NR^1, R^1 is Me, R^2 is Br, **B** is CR^3, R^3 is

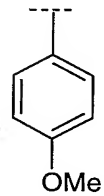


, **K** is N, **L** is CR^5, R^5 is Me, **M** is CR^7, R^7 is Br, Y^1 is O, and **Z** is OR^6, then R^6 is not Me;

and with the further proviso that when **A** is NR^1, R^1 is H, R^2 is Cl, **B** is CR^3, R^3 is Et, **K** is CH, **L** is CH, **M** is CH, Y^1 is O, **Z** is OR^6, then R^6 is not Me;

and with the further proviso that when **A** is NR^1, R^1 is H, R^2 is phenyl, **B** is CR^3, R^3 is phenyl, **K** is CH, **L** is CH, **M** is CR^7, R^7 is Me, Y^1 is O, **Z** is OR^6, then R^6 is not Et;

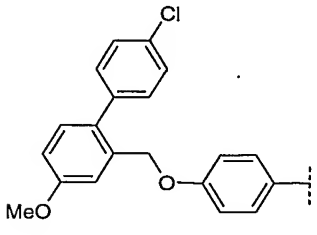
and with the further proviso that when **A** is NR^1, R^1 is H, R^2 is 

, **B** is CR^3, R^3 is 

, **K** is CH, **L** is N, **M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Et;

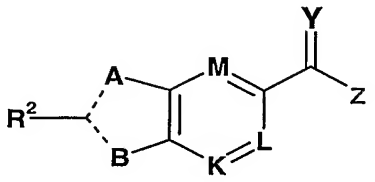
with the further proviso that when **A** is S, R^2 is Br, **B** is CR^3, R^3 is Me, **K** is CH, **L** is CH, **M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Me;

and with the further proviso that, when **A** is NR^1, R^1 is H, R^2 is:



, **B** is NR^3, R^3 is cyclohexyl, **K, L, M** is CH, Y^1 is O, **Z** is OR^6, then R^6 is not H.

Alternatively, in a first aspect of the invention, there is provided a compound represented by Formula Ia:



(Ia)

wherein:

A is O, S, NR^1, or CR^1;

B is NR^3 or CR^3;

R^1 is selected from the group consisting of: H, (C_{1-6})alkyl, benzyl, $(C_{1-6}$ alkyl)-$(C_{6-10}$aryl), $(C_{1-6}$ alkyl)-5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, and 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said benzyl and said heteroatom are optionally substituted with from 1 to 4 substituents selected from the group consisting of: COOH, $COO(C_{1-6}$ alkyl), halogen, and $(C_{1-6}$ alkyl);

R^2 is selected from the group consisting of: H, halogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, pyridine-N-oxide , and 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S,

said phenyl, heterocycle and heterobicycle being optionally substituted with from 1 to 4 substituents selected from the group consisting of: halogen, $C(halogen)_3$, (C_{1-6})alkyl, OH, $O(C_{1-6}$ alkyl), NH_2, and $N(C_{1-6}$ alkyl)$_2$;

R^3 is selected from the group consisting of: 5-, 6- or 7-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, norbornane, (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-$(C_{1-6}$ alkyl);

M is N, CR^4, or COR^5, wherein R^4 is selected from the group consisting of: H, halogen, and $(C_{1-6}$ alkyl); and R^5 is selected from the group consisting of: H and $(C_{1-6}$ alkyl);

K and **L** is N or CH;

----- represents either a single or a double bond;

Y is O;

Z is OR^6 or NR^6R^{6a}, wherein R^6 is selected from the group consisting of: H, (C_{1-6})alkyl, wherein said alkyl is optionally substituted with from 1 to 4 substituents selected from: OH, COOH, $COO(C_{1-6})$alkyl, (C_{1-6})alkyl, said alkyl being optionally substituted with from 1 to 4 substituents selected from: COOH, $NHCO(C_{1-6}$ alkyl), NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$;

or a salt thereof.

In a third aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of RNA dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV.

In a fourth aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

In a fifth aspect of the invention, there is provided a method of treating or preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In a sixth aspect of the invention, there is provided a pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

According to a specific embodiment, the pharmaceutical compositions of this invention comprise an additional immunomodulatory agent. Examples of additional immunomodulatory agents include but are not limited to, α-, β-, δ- γ-, and ω-interferons.

According to an alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an antiviral agent. Examples of antiviral agents include, ribavirin and amantadine.

According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise other inhibitors of HCV polymerase.

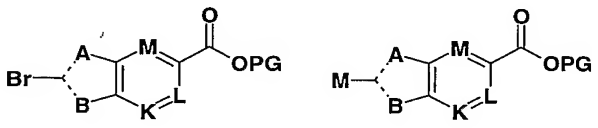
According to yet another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an inhibitor of other targets in the HCV life cycle, such as helicase, polymerase, metalloprotease or IRES.

In a seventh aspect of the invention, there is provided a use of a compound of formula I, for the manufacture of a medicament for the treatment of HCV infection.

In an eighth aspect of the invention, there is provided a use of a compound of formula I, as an HCV polymerase inhibitor.

In a ninth aspect of the invention, there is provided a method of treating or preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in combination with another anti-HCV agent.

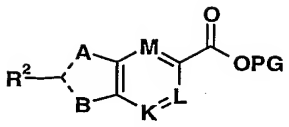
In a tenth aspect of the invention, there is provided an intermediate of formula (1a) or (1b):



1a or 1b

wherein **A, B, K, L**, and **M** are as described herein and **PG** is H or a carboxy protecting group.

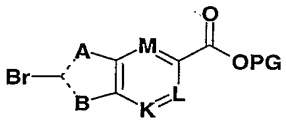
In a eleventh aspect of the invention, there is provided the use of the intermediates of formula (Ia) for producing compounds of formula (iii),



(iii)

wherein **A**, R^2, **B**, **K**, **L**, **M**, and **PG** are as described herein,
comprising:

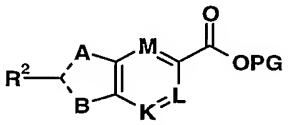
a) coupling, in the presence of a metal catalyst (such as, for example, Pd, Ni, Ru, Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1a):



1a

with R^2-**X**, wherein R^1, R^3, **K**, **L**, **M** and **PG** are as described herein and **X** is (bt not limited to): $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, metal halide, $B(OH)_2$, and $B(O(C_{1-6})alkyl)_2$ to produce compounds of formula (iii).

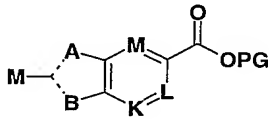
In an alternative to the eleventh aspect of the invention, there is provided the use of intermediate (Ib) for producing compounds of formula (iii),



(iii)

wherein **A**, R^2, **B**, **K**, **L**, **M**, and **PG** are as described herein,
comprising:

b) coupling, in the presence of a metal catalyst (such as, for example, Pd, Ni, Ru, Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1b)



1b

with R^2-**X'**, wherein **X'** is halide, $OSO_2(C_{1-6}alkyl)$, OSO_2Ar, OSO_2CF_3 and the like,

and **M** is a metal such as Li, $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, $B(OH)_2$, $B(OC_{1-6}alkyl)_2$, metal halide, to produce compounds of formula (iii).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following definitions apply unless otherwise noted:

As used herein, the terms "(C_{1-3}) alkyl", "(C_{1-4}) alkyl" or "(C_{1-6}) alkyl", either alone or in combination with another radical, are intended to mean acyclic straight or branched chain alkyl radicals containing up to three, four and six carbon atoms respectively. Examples of such radicals include methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl.

As used herein, the term "(C_{2-6}) alkenyl", either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight chain radical containing two to six carbon atoms.

As used herein, the term (C_{2-6}) alkynyl" either alone or in combination with another group, is intended to mean an unsaturated, acyclic straight chain sp hybridized radical containing 2 to six carbon atoms.

As used herein. the term "(C_{3-7}) cycloalkyl", either alone or in combination with another radical, means a cycloalkyl radical containing from three to seven carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "(C_{5-7})cycloalkenyl", either alone or in combination with another radical, means an unsaturated cyclic radical containing five to seven carbon atoms.

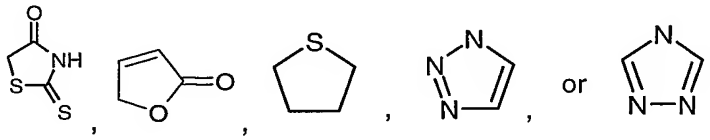
As used herein, the term "carboxy protecting group" defines protecting groups that can be used during coupling and are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosures of which are hereby incorporated by reference.

The α-carboxyl group of the C-terminal residue is usually protected as an ester (CPG) that can be cleaved to give the carboxylic acid. Protecting groups that can be used include: 1) alkyl esters such as methyl, trimethylsilylethyl and *t*-butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters.

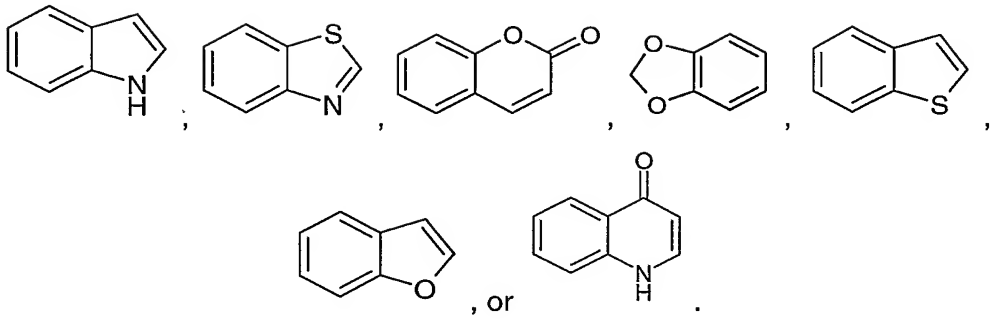
As used herein, the term "aryl", or "6- or 10-membered aryl" either alone or in combination with another radical means aromatic radical containing six or ten carbon atoms, for example phenyl or naphthyl.

As used herein the term heteroatom means O, S or N.

As used herein, the term "heterocycle", either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated (including aromatic) heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Furthermore, "heterobicyclic" as used herein, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterocycles include, but are not limited to, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, coumarin, hydantoin, diazepine, 1H-imidazole, isoxazole, thiazole, tetrazole, piperidine, 1,4-dioxane, 4-morpholine, pyridine, pyridine-N-oxide, pyrimidine, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following heterocycles:



As used herein, the term "9- or 10-membered heterobicycle" or "heterobicycle" either alone or in combination with another radical, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterobicycles include, but are not limited to, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following:



As used herein, the term "**Het**" defines a 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms wherever possible, selected from O, N and S.

As used herein, the term "halo" means a halogen atom and includes fluorine, chlorine, bromine and iodine.

As used herein, the term "haloalkyl" is intended to mean an alkyl that is described above in which each hydrogen atom may be successively replaced by a halogen atom, for example CH_2Br or CF_3.

As used herein, the term "metal halide" is intended to mean any metal that is bonded to a halogen atom for use in a metal-catalyzed cross-coupling reaction. Examples of such metal halides include, but are not limited to, -MgCl, -CuCl, or -ZnCl and the like.

As used herein, the term "OH" refers to a hydroxyl group. It is well known to one skilled in the art that hydroxyl groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, ethers, sulfhydryls, and primary, secondary or tertiary amines.

As used herein, the term "SH" refers to a sulfhydryl group. It is intended within the scope of the present invention that , whenever a "SH" or "S**R**" group is present, it can also be substituted by any other appropriate oxidation state such as S**O**R, SO_2**R**, or SO_3**R**.

It is intended that the term "substituted" when applied in conjunction with a radical having more than one moiety such as C_{1-6}alkyl-aryl, or C_{1-6}alkyl-**Het**, such substitution applies to both moieties i.e. both the alkyl and aryl or **Het** moieties can be substituted with the defined substituents.

As used herein, the term "COOH" refers to a carboxylic acid group. It is well known to one skilled in the art that carboxylic acid groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, esters, amides, boronic acids or tetrazole.

As used herein, the term "functional group equivalent" is intended to mean an element or a substituted derivative thereof, that is replaceable by another element that has similar electronic, hybridization or bonding properties.

As used herein, the term "metal catalyst" is intended to mean a metal such as palladium (0) or palladium (2) that is bonded to a leaving group for use in a cross-coupling reaction. Examples of such palladium catalysts include, but are not limited to, $Pd(Ph_3)_4$, Pd/C, $Pd(OAc)_2$, $PdCl_2$, and the like. Alternative metals that can catalyze cross-coupling reactions include, but are not limited to: $Ni(acac)_2$, $Ni(OAc)_2$, or $NiCl_2$.

As used herein, the term "derivative" is intended to mean "detectable label", "affinity tag" or "photoreactive group". The term "detectable label" refers to any group that may be linked to the polymerase or to a compound of the present invention such that when the compound is associated with the polymerase target, such label allows recognition either directly or indirectly of the compound such that it can be detected, measured and quantified. Examples of such "labels" are intended to include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes and affinity tags such as biotin. Such labels are attached to the compound or to the polymerase by well known methods.

The term "affinity tag" means a ligand (that is linked to the polymerase or to a compound of the present invention) whose strong affinity for a receptor can be

used to extract from a solution the entity to which the ligand is attached. Examples of such ligands include biotin or a derivative thereof, a histidine polypeptide, a polyarginine, an amylose sugar moiety or a defined epitope recognizable by a specific antibody. Such affinity tags are attached to the compound or to the polymerase by well-known methods.

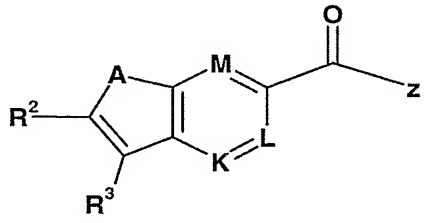
The term "photoreactive group" means a group that is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Examples of such groups include, but are not limited to, benzophenones, azides, and the like.

As used herein, the term "pharmaceutically acceptable salt" includes those derived from pharmaceutically acceptable bases and is non-toxic. Examples of suitable bases include choline, ethanolamine and ethylenediamine. Na^+, K^+, and Ca^{++} salts are also contemplated to be within the scope of the invention (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19, incorporated herein by reference).

Preferred embodiments

A:

Preferably, compounds of the present invention have the following formula (II):

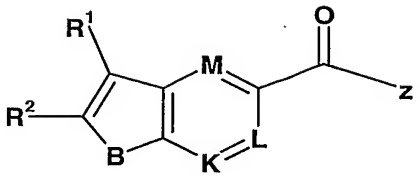


(II)

wherein, preferably, **A** is O, S, or NR^1.

Preferably, **A** is NR^1.

Preferably, compounds of the present invention have the following formula (III):

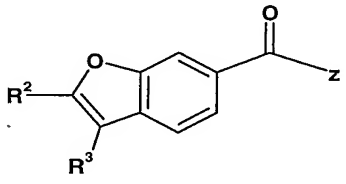


(III)

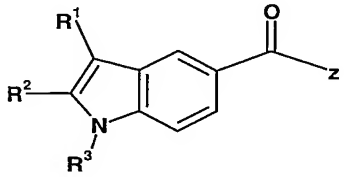
wherein, preferably, **B** is NR^3.

With respect to compounds of formula (II) and (III), preferably, **M, K** and **L** is CH or N. More preferably, **M, K** and **L** is CH.

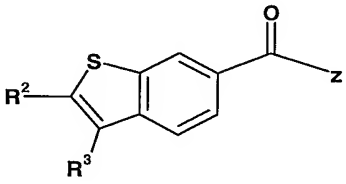
More preferably, compounds of the present invention have the following formulae:



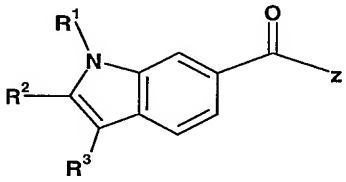
IIa



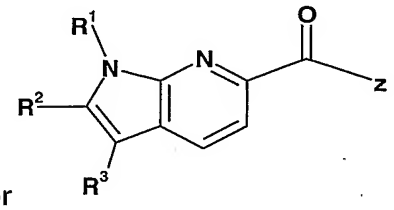
IIIa



IIb



IIc



or

IId

R^1:

Preferably R^1 is selected from the group consisting of: H or (C_{1-6})alkyl. More preferably, R^1 is H, CH_3, isopropyl, or isobutyl. Even more preferably, R^1 is H or CH_3. Most preferably, R^1 is CH_3.

R^2:

Preferably, R^2 is selected from: H, halogen, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**; wherein (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, aryl or **Het** is optionally substituted with R^{20}, wherein R^{20} is defined as:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl,

Het, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with

R^{150};

l) aryl, **Het,** (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with R^{150};

wherein R^{150} is preferably:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or

- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het** and heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, or (C_{3-7})cycloalkyl, and R^{112} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated

heterocycle;

said alkyl, cycloalkyl, and heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from:

halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, R^2 is selected from: aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, N_3, or

a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}$

alkyl);

b) (C_{1-6})alkoxy;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; being optionally substituted with halogen or:

- OR^{161} or $N(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle;

f) $NHCOR^{117}$ wherein R^{117} is (C_{1-6})alkyl, $O(C_{1-6})$alkyl or $O(C_{3-7})$cycloalkyl;

i) CO-aryl; and

k) $CONH_2$, $CONH(C_{1-6}alkyl)$, $CON(C_{1-6}alkyl)_2$, CONH-aryl, or $CONHC_{1-6}$alkyl-aryl.

Still, more preferably, R^2 is aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, or

a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}alkyl)$;

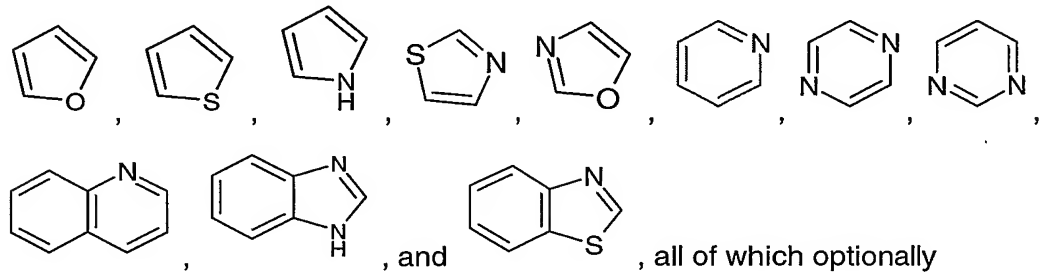
b) (C_{1-6})alkoxy; and

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; or being optionally substituted with halogen or:

- OR^{161} or $N(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, or both R^{162} are covalently bonded together and to the nitrogen to which they are

attached to form a nitrogen-containing heterocycle.

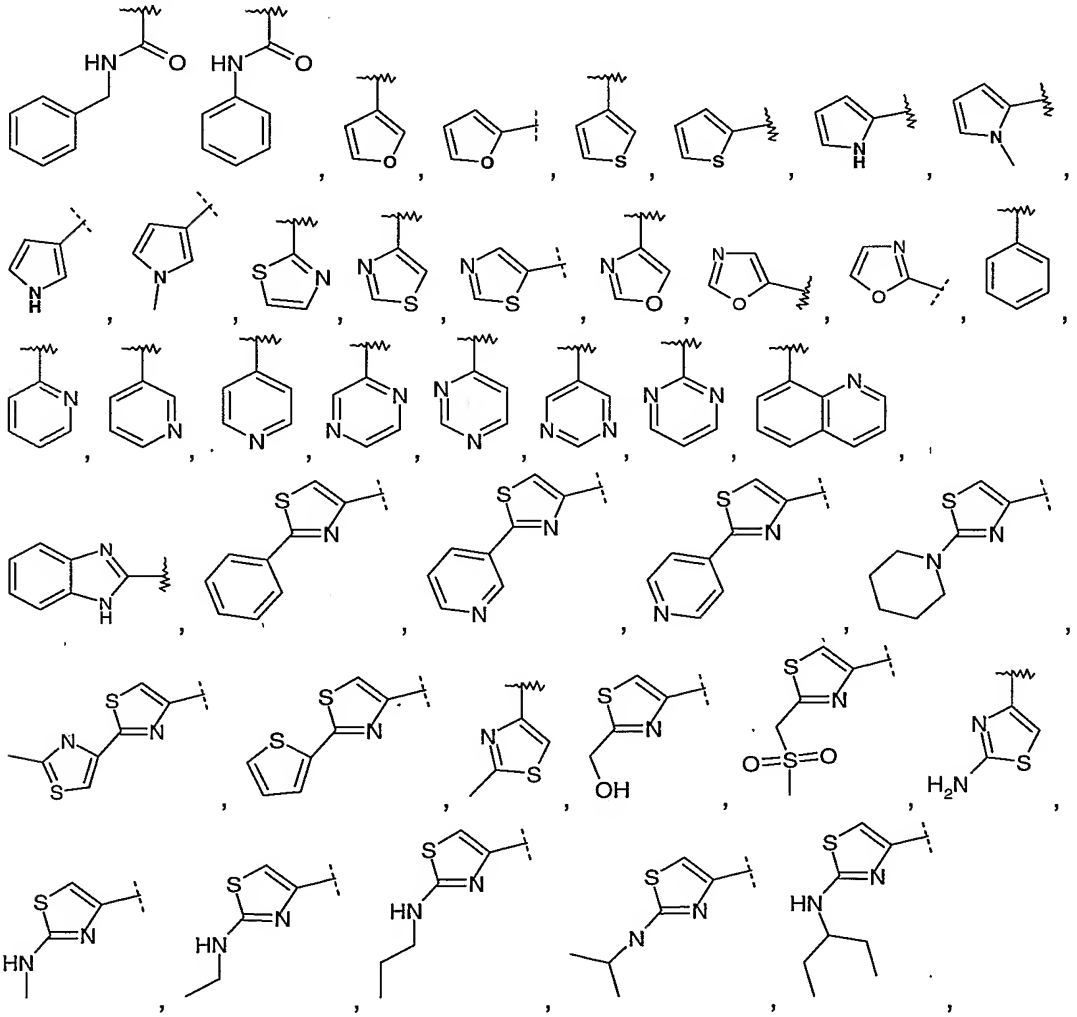
Even more preferably, R^2 is phenyl or a heterocycle selected from:

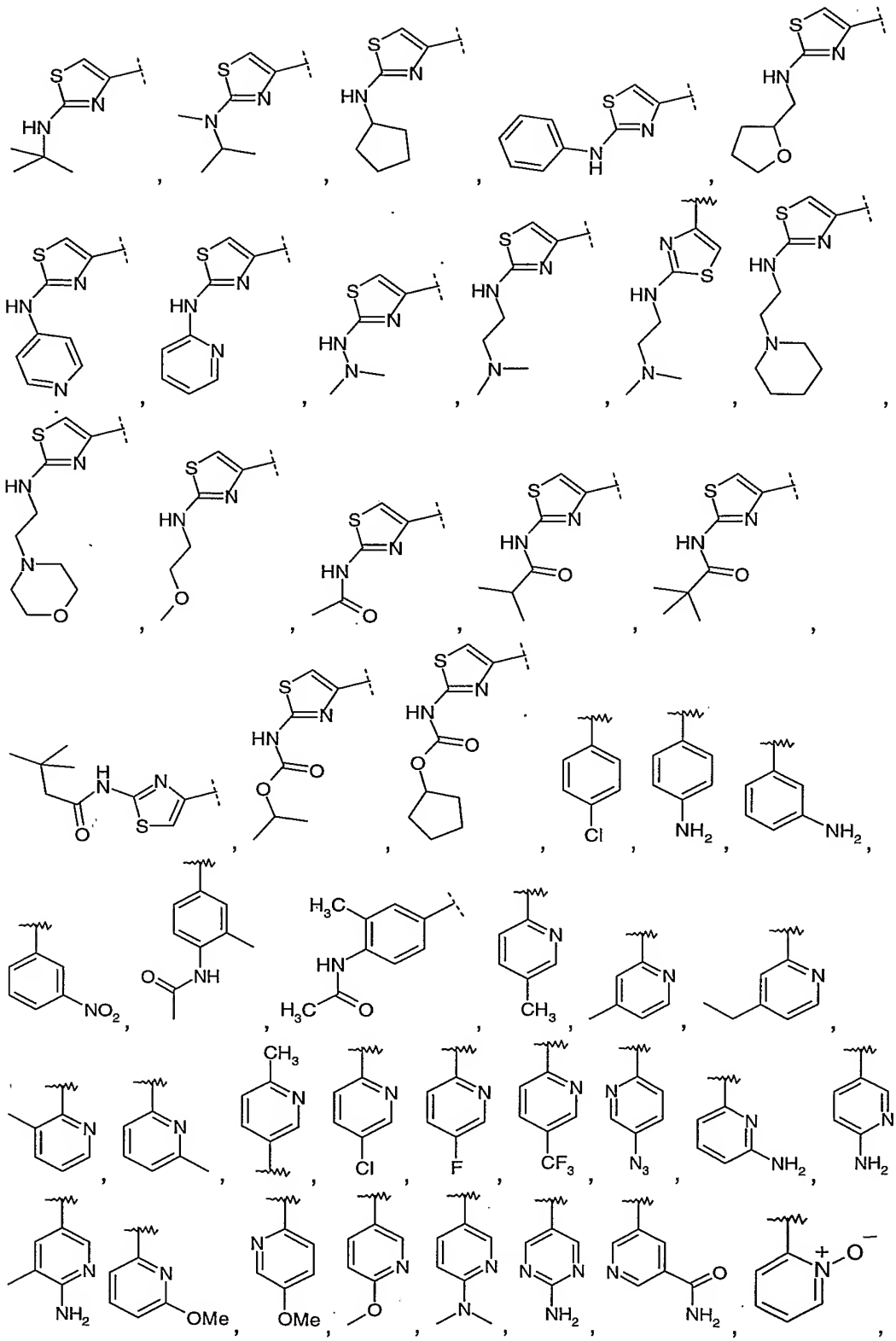


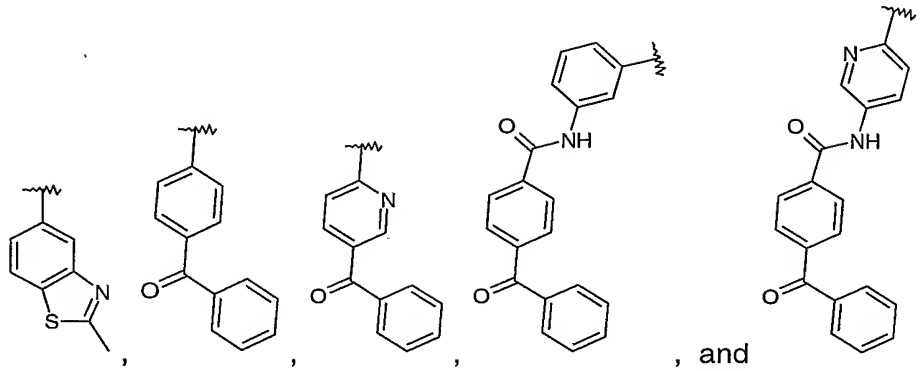
, and , all of which optionally substituted as defined above.

Even more preferably, R^2 is selected from the group consisting of:

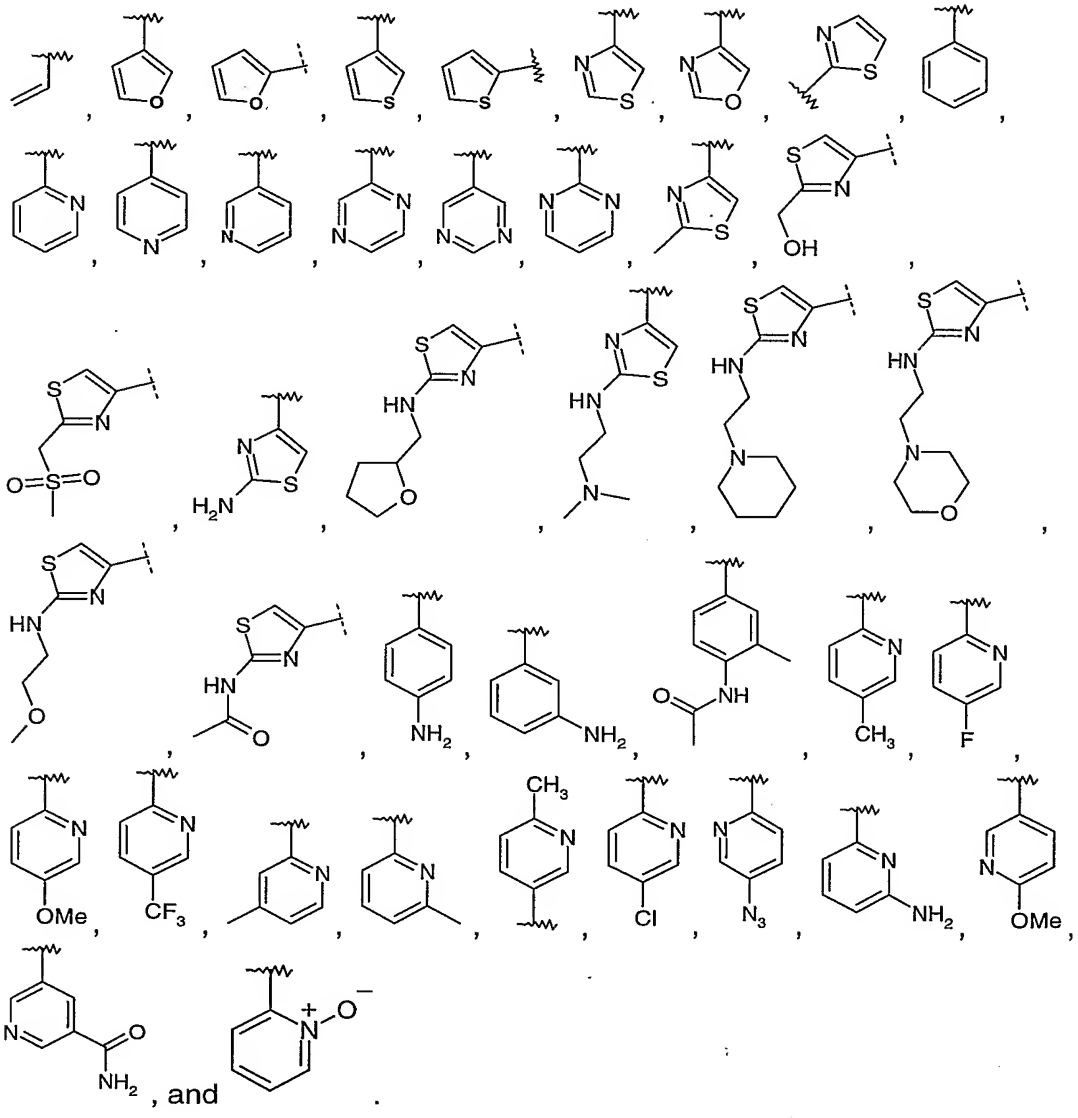
H, Br, $CH=CH_2$,



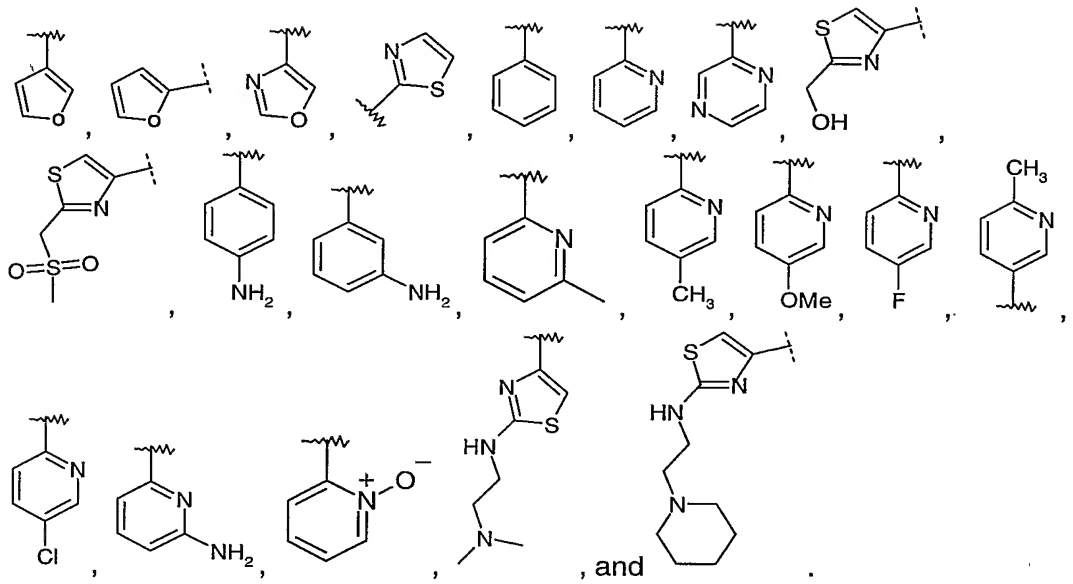



, , , , and .

Still more preferably, R^2 is selected from:


, and .

Most preferably, R^2 is selected from:



<u>R^3:</u>

Preferably, R^3 is selected from (C_{3-7})cycloalkyl, (C_{3-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, or **Het**. More preferably, R^3 is (C_{3-7})cycloalkyl. Most preferably, R^3 is cyclopentyl, or cyclohexyl.

<u>Y:</u>

Preferably Y^1 is O.

<u>Z:</u>

Preferably, **Z** is OR^6, wherein R^6 is H, (C_{1-6})alkyl being optionally substituted with: halo, hydroxy, carboxy, amino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, and C_{1-6} alkylamino; or R^6 is C_{1-6} alkylaryl optionally substituted with: halogen, cyano, nitro, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}alkanoyl, $-(CH_2)_{1-6}-COOR^7$, $-(CH_2)_{1-6}-CONR^7R^8$, $-(CH_2)_{1-6}-NR^7R^8$, $-(CH_2)_{1-6}-NR^7COR^8$, $-(CH_2)_{1-6}-NHSO_2R^7$, $-(CH_2)_{1-6}-OR^7$, $-(CH_2)_{1-6}-SR^7$, $-(CH_2)_{1-6}-SO_2R^7$, and $-(CH_2)_{1-6}-SO_2NR^7R^8$, wherein each R^7 and each R^8 is H or C_{1-6} alkyl,

or **Z** is NR^9R^{10} wherein each of R^9 and R^{10} is selected from: H, C_{1-6}alkoxy, or C_{1-6}alkyl optionally substituted with halo, hydroxy, carboxy, amino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, and C_{1-6} alkylamino;

More preferably, **Z** is OH or O(C_{1-6}alkyl) or **Z** is NR^9R^{10} wherein R^9 is preferably H and R^{10} is preferably H or C_{1-6}alkyl.

Most preferably, **Z** is OH.

Specific embodiments

Included within the scope of this invention are all compounds of formula I as presented in Tables 1 and 2.

Polymerase activity

The ability of the compounds of formula (I) to inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV can be demonstrated by any assay capable of measuring RNA dependent RNA polymerase activity. A suitable assay is described in the examples.

Specificity for RNA dependent RNA polymerase activity

To demonstrate that the compounds of the invention act by specific inhibition of HCV polymerase, the compounds may be tested for inhibitory activity in a DNA dependent RNA polymerase assay.

When a compound of formula (I), or one of its therapeutically acceptable salts, is employed as an antiviral agent, it is administered orally, topically or systemically to mammals, e.g. humans, rabbits or mice, in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice.

For oral administration, the compound or a therapeutically acceptable salt thereof can be formulated in unit dosage forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier.

For topical administration, the compound can be formulated in pharmaceutically accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the

active agent. Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of formula (I) is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in pharmaceutical texts, e.g. in "Remington's The Science and Practice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstance is reached. In general, the compound of formula I is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound or a therapeutically acceptable salt is administered in the range of 10 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 150 mg per kilogram.

For systemic administration, the compound of formula (I) is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. A dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

When the compositions of this invention comprise a combination of a compound

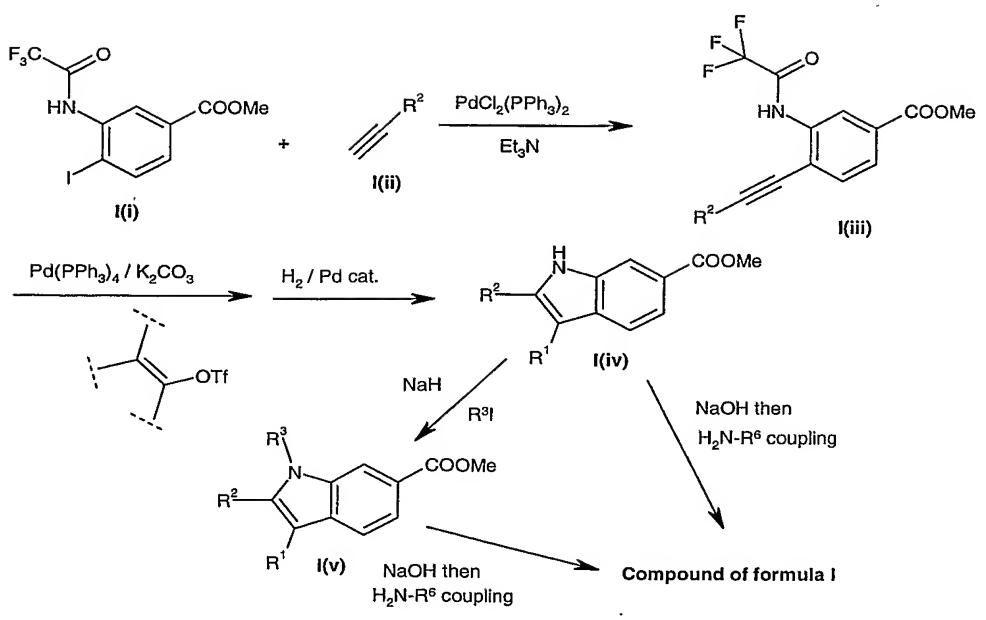
of formula I and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

When these compounds or their pharmaceutically acceptable salts are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit HCV polymerase or to treat or prevent HCV virus infection. Such treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as α-, β-, or γ-interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS5B polymerase; inhibitors of other targets in the HCV life cycle, which include but not limited to, helicase, NS2/3 protease, NS3 protease, or internal ribosome entry site (IRES); or combinations thereof. The additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Methodology and Synthesis

Indole derivatives or analogs according to the present invention can be prepared from known monocyclic aromatic compounds by adapting known literature sequences such as those described by J.W. Ellingboe et al. (*Tet. Lett.* **1997**, *38*, 7963) and S. Cacchi et al. (*Tet. Lett.* **1992**, *33*, 3915). Scheme 1, shown below wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^6}$, **K**, **L**, and **M** are as described herein illustrate how these procedures can be adapted to the synthesis of compounds of formula **1** of this invention.

Scheme 1



In carrying out the route illustrated in Scheme 1, a suitably protected form of 3-trifluoroacetamido-4-iodobenzoic acid **I(i)** is reacted with an alkyne **I(ii)** in the presence of a metal catalyst (e.g. a palladium metal complex such as $PdCl_2(PPh_3)_2$, Pd_2dba_3, $Pd(PPh_3)_4$ and the like), a base (Et_3N, DIEA and the like or an inorganic basic salt including metal carbonates, fluorides and phosphates), and optionally in the presence of an additional phosphine ligand (triaryl or heteroarylphosphine, dppe, dppf, dppp and the like). Suitable solvents for this reaction include DMF, dioxane, THF, DME, toluene, MeCN, DMA and the like at temperatures ranging from 20 °C to 170 °C, or alternatively without solvent by heating the components together. Alternatively, the cross-coupling reaction can be carried out on a suitably protected form of 3-amino-4-iodobenzoate and the amino group can be trifluoroacetylated in the subsequent step as described by J.W. Ellingboe et al. (*Tet. Lett.* **1997**, *38*, 7963).

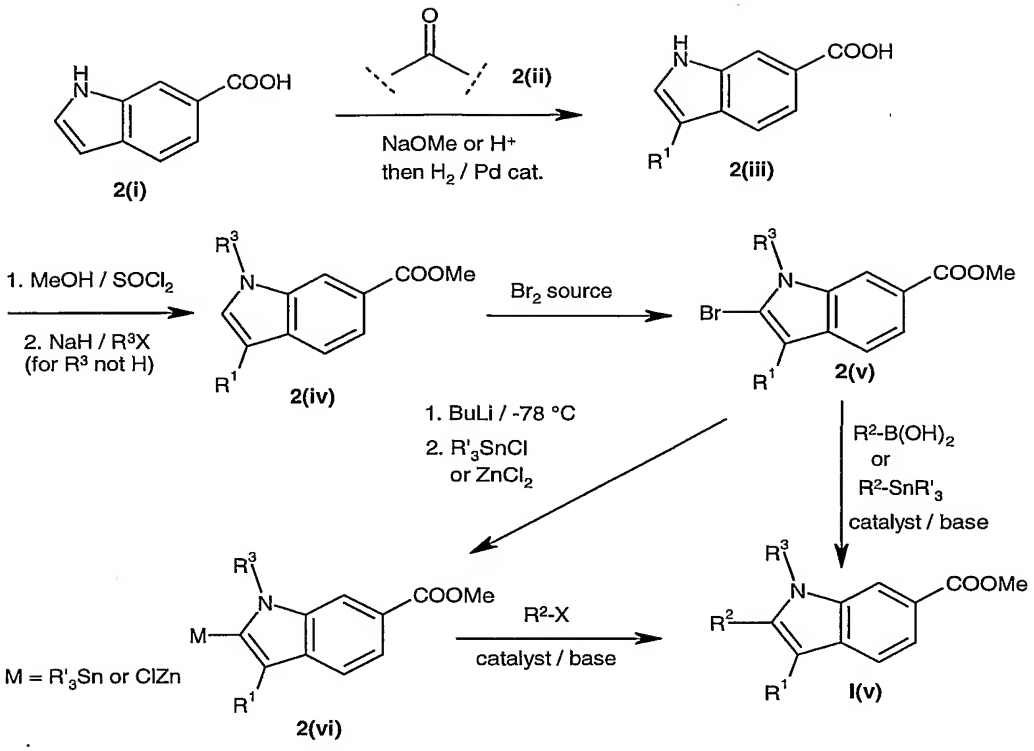
Reaction of the above diarylalkynes **I(iii)** with an enol triflate under cross-coupling conditions similar to those described above gives after hydrogenation of the douple bond, indole derivatives **I(iv)**. Enol triflates are known and can be prepared from the corresponding ketones by following known literature methods (for example, cyclohexene triflate can be prepared from cyclohexanone, triflic anhydride and a hindered organic base such as 2,6-di-*tert*-butyl-4-methylpyridine). The hydrogenation of the double bond originally present in R^1 can be carried out

with hydrogen gas or a hydrogen donor (ammonium formate, formic acid and the like) in the presence of a metal catalyst (preferably Pd) in a suitable solvent (lower alkyl alcohols, THF etc.).

Finally, following hydrolysis of the ester protecting group in **I(iv),** the resulting 6-carboxyindole derivative **I(v)** is converted to compounds of formula **1** by coupling with the appropriate amine of formula H_2N-R^6. Condensation of the 6-indolecarboxylic acid with amines H_2N-R^6 can be accomplished using standard amide bond forming reagents such as TBTU,HATU, BOP,BroP, EDAC, DCC, isobutyl chloroformate and the like, or by activation of the carboxyl group by conversion to the corresponding acid chloride prior to condensation with an amine. Any remaining protecting group is removed following this step to give compounds of formula **1**.

Alternatively, compounds of formula **1** can be prepared by elaboration from a pre-exisitng indole core by following adaptations of literature procedures as described, for example, by P. Gharagozloo et al. (*Tetrahedron* **1996**, *52*, 10185) or K. Freter (*J. Org. Chem.* **1975**, *40*, 2525). Such a methodology is illustrated in Scheme 2:

Scheme 2



In carrying the route illustrated in Scheme 2, commercially available 6-indolecarboxylic acid **2(i),** which can also be prepared according to the method of S. Kamiya et al. (*Chem. Pharm. Bull.* **1995**, *43*, 1692) is used as the starting material. The indole **2(i)** is reacted with a ketone **2(ii)** under basic or acidic aldol-type conditions. Suitable conditions to affect this condensation include strong bases such as alkali metal hydroxides, alkoxides and hydrides in solvents such as lower alkyl alcohols (MeOH, EtOH, *tert*BuOH etc.), THF, dioxane, DMF, DMSO, DMA and the like at reaction temperature ranging from –20 °C to 120 °C. Alternatively, the condensation can be carried out under acid conditions using organic or mineral acids or both. Appropriate conditions include mixtures of AcOH and aqueous phosphoric acid at temperatures ranging from 15°C to 120 °C.

Following protection of the carboxylic acid group in the form of an ester (usually lower alkyl) using known methods, the indole nitrogen can be alkylated with R^3 if desired. Reaction conditions to alkylate the nitrogen of an indole derivative are well known to those skilled in the art and include the use of strong bases such as alkali metal hydrides, hydroxides, amides, alkoxides and alkylmetals, in the appropriate solvent (such as THF, dioxane, DME, DMF, MeCN, DMSO, alcohols

and the like) at temperatures ranging from –78 °C to 140 °C. An electrophilic form of R^3 is used for the alkylation of the indole anion. Such electrophilic species include iodides, bromides, chlorides and sulfonate esters (mesylates, tosylate, brosylate or triflate).

Halogenation (usually bromination, but also iodination) of the 2-position of the indole **2(iv)** gives **2(v)**. Suitable halogenating agents include, for example, elemental bromine, *N*-bromosuccinimide, pyridine tribromide, dibromohydantoin and the corresponding iodo derivatives. Suitable solvents for this reaction are inert to reactive halogenating agents and include for example hydrocarbons, chlorinated hydrocarbons (DCM, CCl_4, $CHCl_3$), ethers (THF, DME, dioxane), acetic acid, ethyl acetate, IPA, and mixtures of these solvents. Reaction temperature ranges from –40 °C to 100 °C. A method of choice to carry out the bromination of indoles as shown in Scheme 2 was described by L. Chu (*Tet. Lett.* **1997**, *38*, 3871).

The 2-bromoindole derivatives **2(v)** can be converted directly to fully substituted key intermediates **I(v)** through a cross-coupling reaction with aryl or heteroaryl boronic acids, boronate esters or trialkylstannane derivatives. These boron or tin organometallic species are from commercial sources or can be prepared by standard literature procedures. Cross-coupling with organoboron reagents can be carried out by any variations of the Suzuki cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd°), triaryl or triheteroarylphosphine ligands, an additive such as an inorganic chloride (e.g. LiCl), and a base (usually an aqueous inorganic base such as sodium or potassium carbonate or phosphate). The reaction is usually carried out in an alcoholic solvent (EtOH), DME, toluene, THF and the like at temperatures ranging from 25 °C to 140 °C.

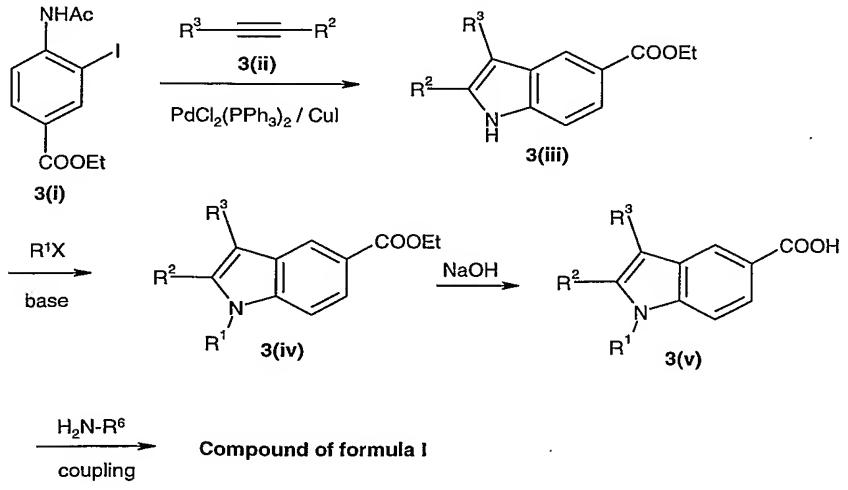
Cross-coupling with tin reagents can be carried out by any variations of the Stille cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd°), triaryl or triheteroaryl phosphine ligands, and an additive such as an inorganic chloride (e.g. LiCl) or iodide (e.g. CuI). Suitable solvents for this reaction include toluene, DMF, THF, DME and the like at temperatures ranging from 25 °C to 140 °C. Intermediate **I(v)** is then converted to compounds of formula **1** as described for Scheme 1.

Alternatively, the 2-bromoindole intermediate **2(v)** can be trans-metallated to an

organotin species (or organozinc) and used in Stille-type cross-coupling reactions under conditions described above. In this case, aromatic and heteroaromatic halides (chlorides, bromides, iodides) or triflates are used to introduce R^2. The conversion of 2-bromoindole derivatives **2(v)** to the corresponding organotin species **2(vi)** is carried out via initial low-temperature (usually –78 ° to –30 °C) halogen-metal exchange using an alkyllithium reagent (e.g. nBuLi or *tert*-BuLi) or using lithium metal. The transient 2-lithioindole species is then trapped with a trialkyltin halide (e.g. nBu_3SnCl or Me_3SnCl). Alternatively, the lithioindole intermediate can be trapped with zinc chloride to form the corresponding organozincate which can also undergo transition metal-catalyzed cross-coupling with aromatic and heteroaromatic halides or triflates as described, for example, by M. Rowley (*J. Med. Chem.* **2001**, *44*, 1603).

The present invention also encompasses compounds of formula **1** where the carboxylic group is in the 5-position of the indole system. The synthesis of such compounds is based on adaptation of literature procedures and is depicted in Scheme 3:

Scheme 3



In carrying out the synthetic route illustrated in Scheme 3, ethyl 4-acetamido-3-iodobenzoate **3(i)** undergoes metal catalyzed cross-coupling with an alkyne **3(ii)** to give a 2,3-disubstituted-5-indolecarboxylate **3(iii)** according to an adaptation of a procedure described by A. Bedeschi et al. (*Tet. Lett.* **1997**, *38*, 2307). The indole derivative **3(iii)** is then alkylated on nitrogen with electrophilic R^1 groups

(halides, sulfonate esters) under the action of a base such as alkali metal hydroxides, fluorides, hydrides amides, alkyllithium, phosphabases and the like, to give **3(iv).** Suitable solvents for this alkylation include DMF, DMA, DMSO, MeCN, THF, dioxane, DME and the like. Following saponification of the ester group with an alkaline solution, the resulting 5-indolecarboxylic acid derivative **3(v)** is coupled to H_2N-$\mathbf{R^6}$ using an amide bond forming reagent as described previously (Scheme 1), to give compounds of formula I.

EXAMPLES

The present invention is illustrated in further detail by the following non-limiting examples. All reactions were performed in a nitrogen or argon atmosphere. Temperatures are given in degrees Celsius. Flash chromatography was performed on silica gel. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Mass spectral analyses were recorded using electrospray mass spectrometry. Abbreviations or symbols used herein include:

DIEA: diisopropylethylamine;

DMAP: 4-(dimethylamino)pyridine;

DMSO: dimethylsulfoxide;

DMF: N,N-dimethylformamide;

Et: ethyl;

EtOAc: ethyl acetate;

Et_2O: diethyl ether;

HPLC: high performance liquid chromatography;

^{i}Pr: isopropyl

Me: methyl;

MeOH: Methanol;

MeCN: acetonitrile;

Ph: phenyl;

TBE: tris-borate-EDTA;

TBTU: 2-(*1H*-benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate;

TFA: trifluoroacetic acid;

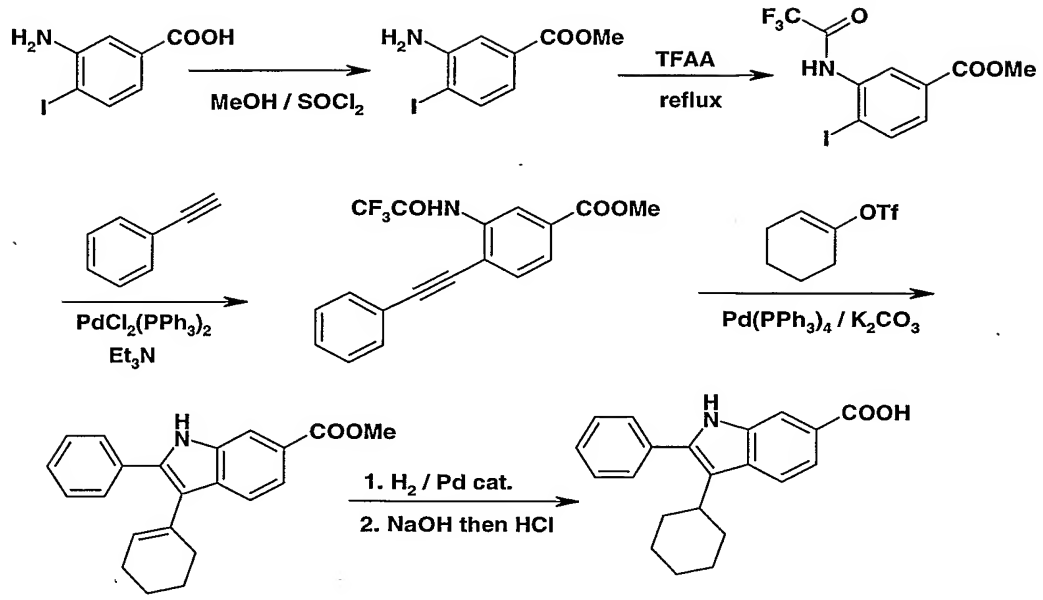
TFAA: trifluoroacetic anhydride;

THF: tetrahydrofuran;

MS (ES): electrospray mass spectrometry;
PFU: plaque forming units;
DEPC: diethyl pyrocarbonate;
DTT: dithiothreitol
EDTA: ethylenediaminetetraacetate
HATU: O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
BOP: benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
EDAC: see ECD
DCC: 1,3-Dicyclohexyl carbodiimide
HOBt: 1-Hydroxybenzotriazole
ES^+: electro spray (positive ionization)
ES^-: electro spray (negative ionization)
DCM: dichloromethane
TBME: *tert*-butylmethyl ether
TLC: thin layer chromatography
AcOH: acetic acid
EtOH: ethanol
DBU: 1,8-diazabicyclo[5.4.0]under-7-ene
BOC: *tert*-butyloxycarbonyl
Cbz: carbobenzyloxy carbonyl
^{i}PrOH: isopropanol
NMP: N-methylpyrrolidone
EDC: 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride
RNAsin: A ribonuclease inhibitor marketed by Promega Corporation
Tris: 2-amino-2-hydroxymethyl-1,3-propanediol
UMP: uridine 5'-monophosphate
UTP: uridine 5'-triphosphate
IPA: isopropyl acetate

Examples 1-22 illustrate methods of synthesis of representative compounds of this invention.

EXAMPLE 1



Methyl 3-amino-4-iodobenzoate:

3-Amino-4-iodobenzoic acid (13.35 g, 50.8 mmol) was added to MeOH (150mL) and $SOCl_2$ (4.8 mL, 65.8 mmol, 1.3 equivalent) was added. The mixture was refluxed for 3 h and then volatiles were removed under reduced pressure. The residue was co-evaporated three times with MeOH and dried in vacuo (15.23 g).

Methyl 3-trifluoroacetamido-4-iodobenzoate:

The aniline derivative from above (14.53 g, 52 mmol) was dissolved in DCM (200 mL) and TFAA (15 mL, 104 mmol) was added. The dark purple solution was refluxed overnight. Volatiles were removed under reduced pressure and the residue was passed through a short pad of silica gel using DCM as eluent. The desired product was obtained as a pink solid (13.81 g).

4-Phenylethynyl-3-(2,2,2-trifluoro-ethanoylamino)-benzoic acid methyl ester:

The iodide from above (0.742 g, 2 mmol), phenylacetylene (0.37 mL, 3.9 mmol, 1.7 equivalent) and Et_3N (6 mL) were charged in a dry flask under argon. $PdCl_2(PPh_3)_2$ (0.241 g, 0.3 mmol) was added and the mixture was stirred at room temperature until judged complete by HPLC analysis (~5 h). The reaction mixture

was concentrated to half volume under reduced pressure and diluted with water (80 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the organic extract washed with 5% HCl (100 mL), after (100 mL) and brine (40 mL). After drying over $MgSO_4$, the residue was purified by flash chromatography using 20% EtOAc – hexane as eluent to give the desired cross-coupled alkyne as a tan solid (0.442 g).

Methyl 3-(cyclohexenyl)-2-phenylindole 6-carboxylate:

A flame-dried flask was charged with finely powdered anhydrous K_2CO_3 (0.153 g, 1.1 mmol) and the alkyne derivative from above (0.390 g, 1.1 mmol). Dry DMF (4 mL) was added and the suspension degassed with a stream of argon. The enol triflate derived from cyclohexanone, prepared following the procedure described by A.G. Martinez, M. Hanack et al. (*J. Heterocyclic Chem.* **1988**, *25*, 1237 or equivalent methods described in the literature, (0.802 g, 3.3 mmol, 3 equivalents) was added followed by $Pd(PPh_3)_4$ (0.086 g, 0.07 mmol) and the mixture was stirred for 8 h at room temperature. DMF was removed under vacuum and the residue purified by flash chromatography using DCM as eluent (0.260 g).

Methyl 3-cyclohexyl-2-phenylindole-6-carboxylate:

The material from above was hydrogenated (1 atm H_2 gas) over 20% $Pd(OH)_2$ in the usual manner, using MeOH as solvent. The desired cyclohexane indole was isolated after filtration of the catalyst.

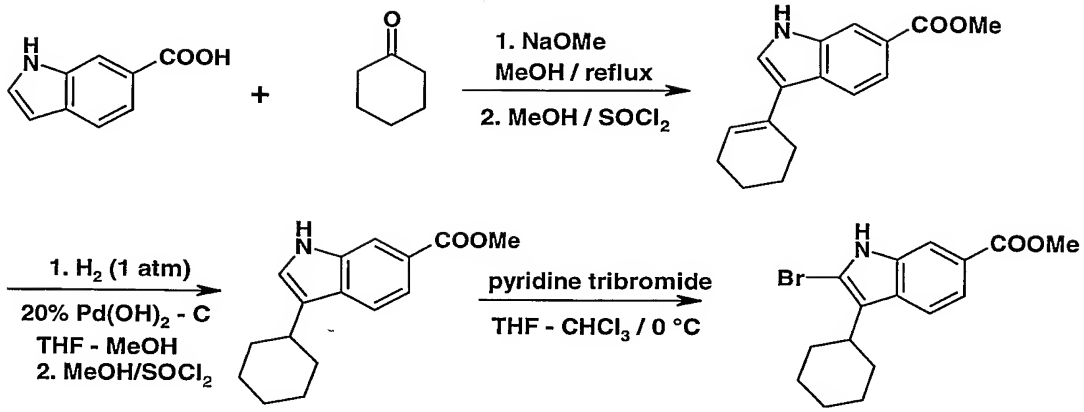
3-Cylohexyl-2-phenylindole-6-carboxylic acid:

The methyl ester from above (0.154 g, 0.15 mmol) was refluxed overnight in a mixture of MeOH (10 mL) and 2N NaOH (6 mL) until complete hydrolysis had occurred as shown by HPLC analysis. After cooling to room temperature, 2N HCl (5 mL) was added followed by AcOH to pH 7. MeOH was removed under reduced pressure, water (50 mL) was added and the product extracted with EtOAc. The extract was washed with water an brine, and dried ($MgSO_4$). Removal of volatiles under reduced pressure gave the title indole carboxylic acid as a light-orange solid (0.149 g).

Following the same procedure but using 2-ethynylpyridine instead of phenylacetylene, 3-cyclohexane-2-(2-pyridyl)indole-6-carboxylic acid was

obtained.

EXAMPLE 2:



3-Cyclohexenyl-6-indole carboxylic acid:

A 12 L round-bottomed flask was equipped with a reflux condenser and a mechanical stirrer, and the system was purged with nitrogen gas. 6-Indole carboxylic acid (300.00 g, 1.86 mole, 3 equivalents) was charged into the flask, followed by MeOH (5.5 L). After stirring for 10 min at room temperature, cyclohexanone (579 mL, 5.58 mole) was added. Methanolic sodium methoxide (25% w/w, 2.6 L, 11.37 mole, 6.1 equivalents) was added in portions over 10 min. The mixture was then refluxed for 48 h. After cooling to room temperature, water (4 L) was added and methanol removed under reduced pressure. The residual aqueous phase was acidified to pH 1 with concentrated HCl (~1.2 L). The resulting yellowish precipitate was collected by filtration, washed with water and dried under vacuum at 50 °C. The desired cyclohexane derivative was obtained as a beige solid (451.0g, 100% yield).

3-Cyclohexyl-6-indole carboxylic acid:

The unsaturated derivative from above was hydrogenated for 20 h under 55 psi hydrogen gas pressure over 20% $Pd(OH)_2/C$ (10.25 g) using 1:1 THF – MeOH (2.5 L) as solvent. After filtration of the catalyst, volatiles were removed under reduced pressure and the residue was triturated with hexane. The beige solid was collected by filtration, washed with hexane and dried under vacuum (356.4 g, 78% yield).

Methyl 3-cyclohexyl-6-indole carboxylate:

A 5 L three-necked flask was equipped with a reflux condenser and a mechanical stirrer, and the system was purged with nitrogen gas. The indole carboxylic acid from above (300.00 g, 1.233 mole) was charged into the flask and suspended in MeOH (2 L). Thionyl chloride (5 mL, 0.0685 mole, 0.05 equivalent) was added dropwise and the mixture was refluxed for 48 h. Volatiles were removed under reduced pressure and the residue was triturated with hexane to give a beige solid that was washed with hexane and dried under vacuum (279.6 g, 88% yield).

Methyl-2-bromo-3-cyclohexyl-6-indole carboxylate:

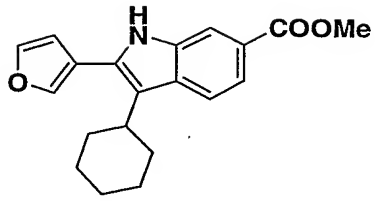
Adapting the procedure of L. Chu (*Tet. Lett.* **1997**, *38*, 3871) methyl 3-cyclohexyl-6-indole carboxylate (4.65 g, 18.07 mmol) was dissolved in a mixture of THF (80 mL) and $CHCl_3$ (80 mL). The solution was cooled in an ice bath and pyridinium bromide perbromide (pyridine tribromide, 7.22 g, 22.6 mmol, 1.25 equivalent) was added. After stirring for 1.5 h at 0 °C, the reaction was judged complete by TLC. It was diluted with $CHCl_3$ (200 mL), washed with 1M $NaHSO_3$ (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL) and brine (50 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue crystallized from TBME – hexane. The desired 2-bromoindole derivative was collected by filtration, washed with hexane and dried (3.45 g). Evaporation of mother liquors gave a red solid that was purified by flash chromatography using 15% EtOAc in hexane yielding an additional 3.62 g of pure material. Total yield was 5.17 g (85% yield).

EXAMPLE 3:

General procedure for the Suzuki cross-coupling of aryl and heteroarylboronic acids with 2-bromoindole derivatives:

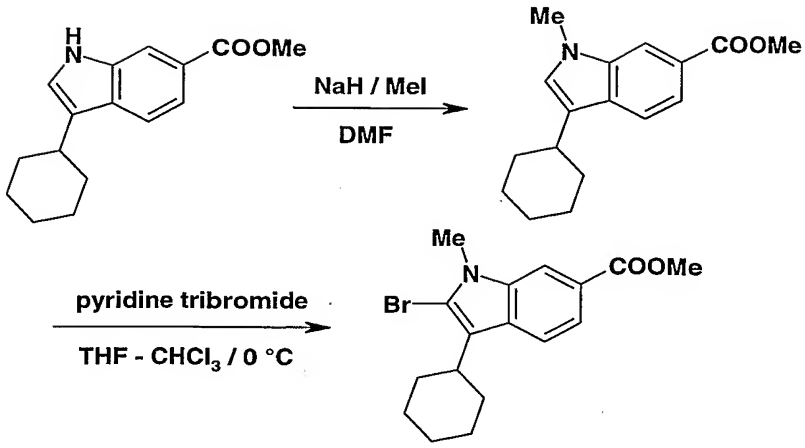
Cross-coupling of aromatic/heteroaromatic boronic acid or ester derivatives with 2-bromoindoles such as the one described in example 2 can be performed using any variations of the standard metal-catalyzed Suzuki cross-coupling reaction as described in the literature and well known to those skilled in the art. The following example serves to illustrate such a process and is non-limiting.

3-Cyclohexyl-2-furan-3-yl-1H-indole-6-carboxylic acid methyl ester:



The 2-bromoindole of example 2 (8.92 g, 26.5 mmol), 3-furanboronic acid (B.P. Roques et al. *J. Heterocycl. Chem.* **1975**, *12*, 195; 4.45 g, 39.79 mmol, 1.5 equivalent) and LiCl (2.25 g, 53 mmol, 2 equivalents) were dissolved in a mixture of EtOH (100 mL) and toluene (100 mL). A 1M aqueous Na_2CO_3 solution (66 mL, 66 mmol) was added and the mixture was degassed with argon for 45 min. $Pd(PPh_3)_4$ (3.06 g, 2.65 mmol, 0.1 equivalent) was added and the mixture stirred overnight at 75-85 °C under argon. Volatiles were removed under reduced pressure and the residue re-dissolved in EtOAc (500 mL). The solution was washed with water, saturated $NaHCO_3$ (100 mL) and brine (100 mL). After drying over a mixture of $MgSO_4$ and decolorizing charcoal, the mixture was filtered and concentrated under reduced pressure. The residual oil was triturated with a mixture of TBME (20 mL) and hexane (40 mL), cooled in ice and the precipitated solid collected by filtration, washed with cold 25% TBME in hexane, and dried (3.09 g). The filtrate and washings from the above trituration were combined, concentrated and purified by flash chromatography using 10-25% EtOAc in hexane to give an additional 4.36 g of product. The total yield of the 2-(3-furyl)indole of example 3 was 8.25 g.

EXAMPLE 4:



Methyl 3-cyclohexyl-1-methyl-6-indole carboxylate:

Methyl 3-cyclohexyl-6-indole carboxylate from example 2 (150.00 g, 0.583 mole) was charged into a 3 L three-necked flask equipped with a mechanical stirrer and purged with nitrogen gas. DMF (1 L) was added and the solution was cooled in an ice-bath. NaH (60% oil dispersion, 30.35 g, 0.759 mole, 1.3 equivalent) was added in small portions (15 min) and the mixture was stirred for 1 h in the cold. Iodomethane (54.5 mL, 0.876 mole, 1.5 equivalent) was added in small portions, maintaining an internal temperature between 5 – 10 °C. The reaction mixture was then stirred overnight at room temperature. The reaction was quenched by pouring into ice-water (3 L), resulting in the formation of a cream-colored precipitate. The material was collected by filtration, washed with water and dried in vacuum at 45 °C (137.3 g, 86% yield).

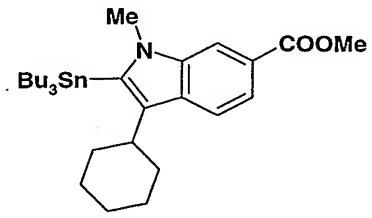
Methyl 2-bromo-3-cyclohexyl-1-methyl-6-indole carboxylate:

The 1-methylindole derivative from above (136.40 g, 0.503 mole) was charged into a 5 L three-necked flask equipped with a mechanical stirrer and purged with nitrogen gas. $CHCl_3$ (750 mL) and THF (750 mL) were added and the solution was cooled to 0 °C. Pyridine tribromide (pyridinium bromide perbromide, 185.13 g, 0.579 mole, 1.15 equivalent) was added in small portions and the mixture was stirred for 1 h at 0 °C. The solvent was removed under reduced pressure at room temperature and the residue dissolved in EtOAc (3 L). The solution was washed with water and brine, dried (decolourising charcoal / $MgSO_4$) and concentrated under reduced pressure. The residue was suspended in TBME and heated to 50 °C. The suspension was stored overnight in the refrigerator and the cream-

coloured crystalline product was collected by filtration. It was washed with TBME and dried in vacuum (134.3 g, 76% yield).

EXAMPLE 5:

Cyclohexyl-methyl-tributylstannanyl-1H-indole-6-carboxylic acid methyl ester:



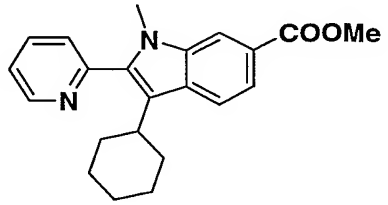
The bromoindole derivative of example 4 (2.70 g, 7.71 mmol) was dissolved in dry THF (40 mL) and the solution was cooled to –78 °C under an argon atmosphere. A solution of nBuLi in hexane (1.4 M, 6.90 mL, 9.64 mmol, 1.25 equivalent) was added dropwise over 15 min and stirring at low temperature was continued for 75 min. To the resulting suspension was added nBu_3SnCl (2.93 mL, 10.8 mmol, 1.4 equivalent) over 5 min. The suspension dissolved and the solution was stirred for 1 h at –78 °C. The reaction mixture was warmed to room temperature and THF removed under reduced pressure. The residue was dissolved in TBME (150 mL), washed with 1:1 brine – water and dried over $MgSO_4$. The material was purified by chromatography on silica gel that was previously deactivated by mixing with a solution of 5% Et_3N in hexane. The same solvent was used as eluent for the chromatography. The title stannane was isolated as a yellow oil (3.42 g, 79 % yield).

EXAMPLE 6:

General procedure for Stille cross-coupling of the 2-stannane indole of example 5 with aromatic/heteroaromatic halides:

Cross-coupling of aromatic/heteroaromatic halides or pseudohalides (preferably bromides, iodides and triflates) with the stannane derivative of example 5 can be performed using any variations of the standard metal-catalyzed Stille cross-coupling reaction as described in the literature. The following example serves to illustrate such a process.

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:

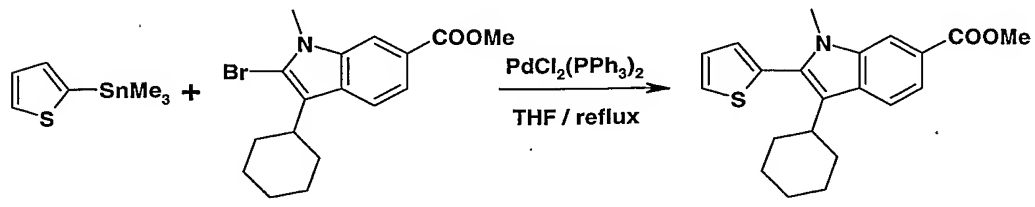


The stannane derivative of example 5 (3.42 g, 6.1 mmol) was dissolved in DMF (10 mL) and CuI (0.116 g, 0.61 mmol, 0.1 equivalent), LiCl (0.517 g, 12.21 mmol, 2 equivalent), triphenylphosphine (0.320 g, 1.22 mmol, 0.2 equivalent) and 2-bromopyridine (0.757 mL, 7.94 mmol, 1.3 equivalent) were added. The solution was degassed with a stream of argon (30 min) and $Pd(PPh_3)_4$ (0.352 g, 0.31 mmol, 0.05 equivalent) was added. After purging with argon for an additional 10 min, the solution was heated and stirred at 100 °C overnight under argon. The DMF was then removed under vacuum and the residue dissolved in EtOAc (150 mL). The solution was washed with 1N NaOH (25 mL) and brine (25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash chromatography eluting with $CHCl_3$ then 5-10% EtOAc in $CHCl_3$ (1.516 g, 71% yield).

EXAMPLE 7:

General procedure for Stille cross-coupling of 2-bromoindoles with aryl or heteroarylstannanes:

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:



The 2-bromoindole derivative of example 4 (0.150 g, 0.428 mmol) and 2-

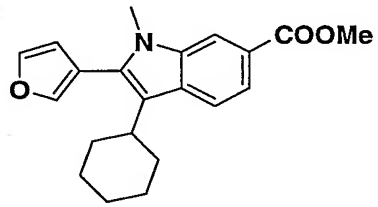
trimethylstannylthiophene (S.F. Thames et al. J. Organometal. Chem. 1972, 38, 29; 0.150 g, 0.61 mmol, 1.4 equivalent) were dissolved in dry THF (7 mL) in a sealed tube, and the solution was degassed with a stream or argon for 30 min. $Pd(Cl)_2(PPh_3)_2$ (0.018 g, 0.026 mmol, 0.06 equivalent was added and the tube sealed. The solution was heated to 80 °C for 40 h. The reaction mixture was cooled to room temperature, EtOAc (10 mL) was added and the suspension filtered. After evaporation of the solvent, the residue was re-submitted to the reaction conditions for an additional 20 h, with fresh 2-stannylthiophene (0.150 g, 0.61 mmol) and catalyst (0.020 g). After cooling to room temperature and filtration of solids, the solvent was evaporated and the residue purified by flash chromatography using 15-100% $CHCl_3$ in hexane as eluent (0.133 g, 88% yield).

The same procedure can be used to couple stannane derivatives to the 2-bromoindole of Example 2.

EXAMPLE 8:

General procedure for the N-alkylation of 2-aryl and 2-heteroaryl-6-indole carboxylates:

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:



NaH (60% oil dispersion, 0.186 g, 4.64 mmol, 1.5 equivalent) was washed with hexane (20 mL) to remove the oil and then re-suspended in DMF (5 mL). After cooling to 0 °C in an ice bath, the indole derivative of example 3 (1.000 g, 3.09 mmol) was added dropwise as a solution in DMF (3 mL + 2 mL rinse). After stirring for 15 min, iodomethane (0.385 mL, 6.18 mmol, 2 equivalents) was added in one portion and the mixture was stirred for 2 h in the cold and an additional 2 h at room temperature. The reaction was then quenched by addition of 1N HCl (1 mL) and diluted with TBME (100 mL). The solution was washed with 1N HCl (25 mL) and dried ($MgSO_4$). After removal of volatiles under reduced pressure, the residue was purified by flash chromatography using 5-10% EtOAc in hexane as

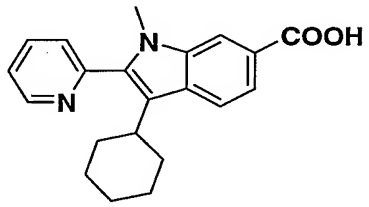
eluent to give the title compound as a white solid (0.903 g, 86% yield).
Other *N*-alkylindole derivatives within the scope of this invention could be prepared from the appropriate electrophiles (e.g. EtI, iPrI, iBuI, BnBr) using a similar procedure.

EXAMPLE 9:

General procedure for the saponification of 6-indolecarboxylates to the corresponding free carboxylic acids:

This procedure applies to both indole and *N*-methylindole carboxylates.

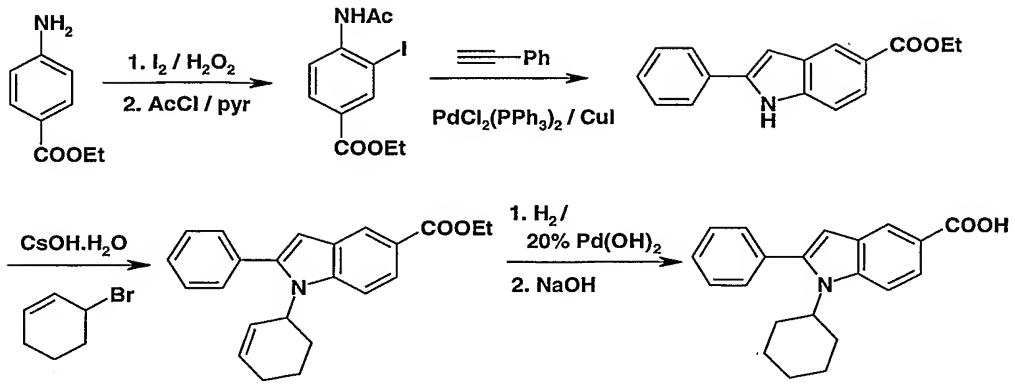
3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid:



The 6-indole carboxylate of example 6 (1.517 g, 4.35 mmol) was dissolved in DMSO (8 mL) and 5N NaOH (4.4 mL) was added. The mixture was stirred at 50 °C for 30 min. The solution was then cooled to room temperature and added dropwise to water (15 mL). Insoluble black impurities were removed by filtration and AcOH (2 mL) was added dropwise to the filtrate. The white precipitate that formed was collected by filtration, washed with water and dried (1.37 g, 94% yield).

EXAMPLE 10:

1-Cyclohexyl-2-phenyl-1H-indole-5-carboxylic acid:



Ethyl 4-amino-3-iodobenzoate:

Ethyl 4-aminobenzoate (15.00 g, 91 mmol) and iodine (11.80 g, 46.5 mmol) were mixed with water (80 mL) and chlorobenzene (4.60 g, 41 mmol). The mixture was stirred while the temperature was gradually raised to 90 °C over 30 min. Hydrogen peroxide (30%, 50 mL) was added over 10 h at 90 °C. After stirring at that temperature for an additional 6 h, the mixture was cooled and the solution decanted from the residual solids. The solids were dissolved in DCM and the solution washed successively with sodium thiosulfate and brine. After drying ($MgSO_4$), the solvent was removed under reduced pressure and the resulting brown solid was triturated with hexane to remove di-iodinated by-products. The desired compound was obtained as a brown solid (22.85 g, 86% yield).

Ethyl 4-acetamido-3-iodobenzoate:

The aniline from above (1.00 g, 3.44 mmol) was dissolved in pyridine (5 mL) and the solution was cooled in ice. AcCl (0.32 mL, 4.47 mmol, 1.3 equivalent) was added dropwise and the mixture was stirred for 1 h at 0 °C and 2 h at room temperature. The reaction mixture was then diluted with 1 N HCl and the product was extracted with TBME (100 mL). The organic phase was washed with 1N HCl (50 mL), dried ($MgSO_4$) and concentrated to give the desired material as a tan-colored solid (1.121 g, 97% yield).

Ethyl 2-phenyl-indole-5-carboxylate:

Following the procedure of A. Bedeschi et al. (*Tet. Lett.* **1997**, *38*, 2307), the acetanilide derivative from above (0.900 g, 2.7 mmol) was reacted with phenylacetylene (0.385 mL, 3.5 mmol, 1.3 equivalent) in the presence of

$PdCl_2(PPh_3)_2$ (10 mole %) and CuI (10 mole %) in a mixture of dioxane (5 mL) and tetramethylguanidine (5 mL). The desired 2-phenylindole (0.589 g, 82% yield) was isolated as a yellow solid after flash chromatography with 15% EtOAc in hexane.

1-Cyclohex-1-enyl-2-phenyl-1H-indole-5-carboxylic acid ethyl ester:

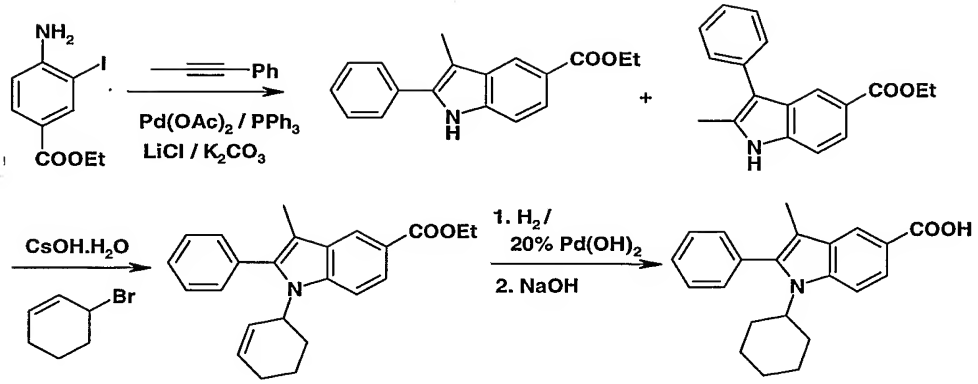
The 2-phenylindole derivative from above (0.265 g, 1.0 mmol) was dissolved in DMF (2 mL) and cesium hydroxide monohydrate (0.208 g, 1.2 mmol, 1.2 equivalent) was added. The solution was cooled in an ice bath and 3-bromocyclohexene (0.193 g, 1.2 mmol, 1.2 equivalent) was added dropwise (5 min) as a solution in DMF (1 mL). The mixture was stirred for 30 min at 0 °C. The reaction was diluted with water (25 mL), extracted with Et_2O (2 x 50 mL) and the extract dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a white foam (0.095 g) that was used without purification in the next step.

1-Cyclohexyl-2-phenyl-1H-indole-5-carboxylic acid:

The crude indole from above was hydrogenated in the usual way (1 atm H_2 gas) in EtOH over 20% $Pd(OH)_2$ on carbon for 20 h at room temperature. After filtration of the catalyst, the EtOH was removed under reduced pressure. The residue was dissolved in a mixture of MeOH (1 mL) and DMSO (1 mL) and 5N NaOH (0.5 mL) was added. The mixture was stirred overnight at 50 °C. The reaction mixture was cooled and water (10 mL) was added. After acidification with 1N HCl, the product was extracted into Et_2O (70 mL) and the solution dried (Na_2SO_4). Evaporation of the solvent gave a green residue consisting of a 2:1 mixture (85 mg) of the desired 1-cyclohexyl-2-phenylindole-5-carboxylic acid and 1,3-dicyclohexyl-2-phenylindole-5-carboxylic acid.

EXAMPLE 11:

1-Cyclohexyl-3-methyl-2-phenyl-1H-indole-5-carboxylic acid:



Ethyl 2-phenyl-3-methyl-indole-5-carboxylate:

Adapting the procedure of H.-C. Zhang (*Tet. Lett.* **1997**, *38*, 2439) ethyl 4-amino-3-iodobenzoate (from example 10, 0.500 g, 1.72 mmol) was dissolved in DMF (5 mL) and LiCl (0.073 g, 1.72 mmol, 1 equivalent), PPh_3 (0.090 g, 0.34 mmol, 0.2 equivalent), K_2CO_3 (1.188 g, 8.6 mmol, 5 equivalents) and phenylpropyne (0.645 mL, 5.76 mmol, 3 equivalents) were added. The solution was degassed by purging with argon for 1 h and palladium acetate (0.039 g, 0.17 mmol, 0.1 equivalent) was added. The mixture was stirred at 80 °C under argon for 20 h. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (50 mL). The extract was washed with brine (3 x 25 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography with 10-15% EtOAc – hexane gave the desired 2-phenyl-3-methyl indole (0.275 g, least polar component) and the 3-phenyl-2-methyl isomer (0.109 g, more polar component).

Ethyl 1-(3-cyclohexenyl)-3-methyl-2-phenylindole-5-carboxylate:

The less polar isomer from above (0.264 g, 0.95 mmol) was dissolved in DMSO (2 mL) and cesium hydroxide monohydrate (0.191 g, 1.14 mmol, 1.2 equivalent) was added followed by 3-bromocyclohexene (0.183 g, 1.14 mmol, 1.2 equivalent in 0.7 mL of DMSO). The mixture was stirred at room temperature for 30 min. Additional CsOH monohydrate (0.400 g, 2.4 equivalents) and 3-bromocyclohexene (0.400 g, 2.4 equivalents) were added and stirring continued for an additional 30 min. Similar amounts of the two reagents were again added and after another 30 min of stirring at room temperature, the reaction was diluted with 1N HCl (6 mL) and water (20 mL). The product was extracted with TBME

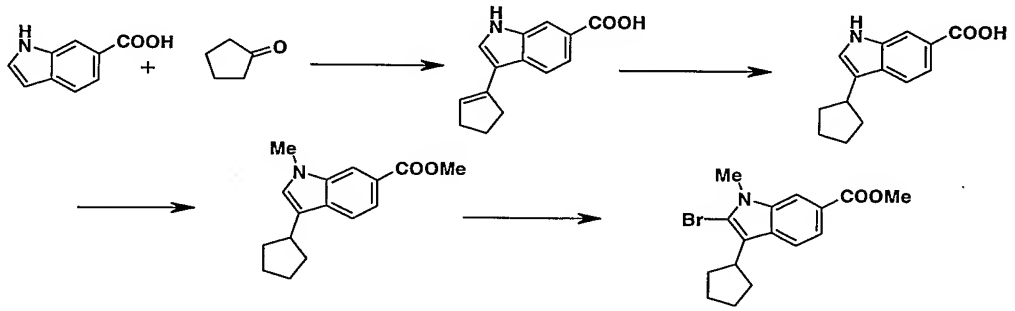
(100 mL), dried ($MgSO_4$) and after concentration under reduced pressure, the residue was purified by flash chromatography using 5-10% EtOAc in hexane as eluent. The desired *N*-alkylated indole was obtained (0.130 g).

Ethyl 1-cyclohexyl-3-methyl-2-phenylindole-5-carboxylate:
The unsaturated product from above was hydrogenated (1 atm H_2 gas) in the usual way over 20% $Pd(OH)_2$ in EtOH at room temperature for 3 h.

1-Cyclohexyl-3-methyl-2-phenyl-1H-indole-5-carboxylic acid:
The hydrogenated material from above was dissolved in a mixture of DMSO (2 mL) and MeOH (2 mL). 5N NaOH (0.5 mL) was added and the mixture was stirred overnight at 60 °C. After dilution with water (40 mL), the product aqueous phase was washed with a 1:1 mixture of Et_2O – hexane (50 mL) and then acidified with 1N HCl to pH 1. The liberated free acid was extracted with diethyl ether (2 x 50 mL) and the extract dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the desired indole as a light brown solid (0.074 g).

EXAMPLE 12:

2-Bromo-3-cyclopentyl-1-methyl-1H-indole-6-carboxylic acid methyl ester:



A 3 L three-necked flask equipped with a mechanical stirrer was charged with indole 6-carboxylic acid (220 g, 1.365 mole) and KOH pellets (764.45 g, 13.65 mole, 10 equivalents). Water (660 mL) and MeOH (660 mL) were added and the mixture heated to 75 °C. Cyclopentanone (603.7 mL, 6.825 mole, 5 equivalents) was added dropwise over 18 h using a pump. The reaction mixture was heated for an additional 3 h (after which the reaction was judged complete by HPLC) and cooled to 0 °C for 1 h. The precipitated potassium salt is collected by filtration, and washed with TBME (2 X 500 mL) to remove cyclopentanone self-condensation products. The brown solid was re-dissolved in water (2.5 L) and the

solution washed with TBME (2 X 1 L). Following acidification to pH 3 with conc. HCl (425 mL), the beige precipitate was collected by filtration, washed with water (2 X 1 L) and dried under vacuum at 70 °C. The crude product weighed 275.9 g (88.9 % mass recovery) and had an homogeneity of 85% (HPLC).

The crude product from above (159.56 g, 0.70 mole) was dissolved in MeOH (750 mL) and 20% $Pd(OH)_2$ on charcoal (8.00 g) was added. The mixture was hydrogenated in a Parr apparatus under 50 psi hydrogen gas for 18 h. After completion, the catalyst was removed by filtration through celite and the solvent removed under reduced pressure. The resulting brown solid was dried at 70 °C under vacuum for 12 h. The crude product (153.2 g) was obtained as a brown solid and was 77% homogeneous by HPLC.

The crude 3-cyclopentylindole-6-carboxylic acid (74.00 g, 0.323 mole) was charged in a 3 L three-necked flask equipped with a mechanical stirrer and a thermometer. The system was purged with nitrogen gas and anhydrous DMF (740 mL) was added. After dissolution on the starting material, anhydrous potassium carbonate (66.91 g, 0.484 mole, 1.5 equivalent) was added and the mixture stirred for 5 minutes. Iodomethane (50 mL, 0.807 mole, 2.5 equivalents) was added and the mixture stirred for 5 h after which HPLC analysis of the reaction mixture indicated 97% conversion to the methyl ester.
The reaction mixture was cooled in an ice bath and sodium hydride (95%, oil-free, 10.10 g, 0.420 mole, 1.3 equivalent) was added in small portions over 3 min (exothermic: 8 °C to 30 °C internal temperature raise). After stirring for an additional 15 min, the cooling bath was removed and stirring continued for 1.5 h at room temperature after which no further progression was observed (HPLC). Additional NaH (1.55 g, 65 mmol, 0.2 equivalent) and iodomethane (1.0 mL, 16 mmol, 0.05 equivalent) were added and after stirring for 15 min, the reaction was judged complete by HPLC (96% N-methylated).
The reaction mixture was slowly (2 min) poured into water (4 L) with vigorous stirring and after 10 min, acidified to pH <2 with conc. HCl (85 mL). The mixture was stirred for 5 min to allow complete conversion of any remaining potassium carbonate and bicarbonate to the more soluble chloride. The pH was adjusted to ~7 with 4N NaOH (40 mL) and the mixture stirred overnight at room temperature. The precipitated material was collected by filtration, washed with water (600 mL)

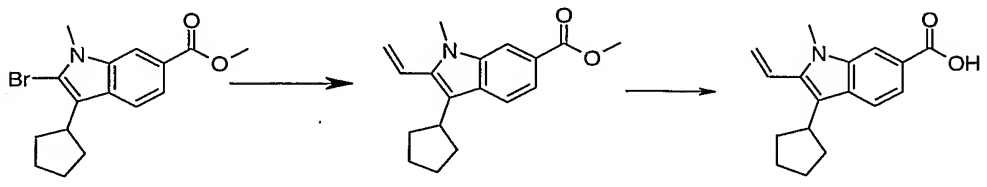
and dried at 60 °C under vacuum. The crude product (79% homogeneity by HPLC) was obtained as a brown solid (72.9 g).

The crude material from above is triturated with a minimal amount of MeOH to remove a series of minor impurities. The solid was then collected by filtration and dissolved in a minimal amount of hot EtOAc. After cooling to room temperature, hexane was added (5 X volume) and the mixture cooled in ice and filtered. The filtrate was then evaporated to dryness to give the desired product.

The *N*-methylindole from above (10.60 g, 41.2 mmol) was dissolved in isopropyl acetate (150 mL) and sodium acetate (5.07 g, 62 mmol, 1.5 equivalent) was added. The suspension was cooled in an ice bath and bromine (2.217 mL, 43.3 mmol, 1.05 equivalent) was added dropwise over 2 min. The pale amber suspension turned dark red (exotherm from 5 °C to 13 °C). It was stirred for 1 h at 0 °C. The reaction was completed by adding additional bromine (0.21 mL, 4.2 mmol, 0.10 equivalent) as shown by HPLC analysis. The reaction was then quenched by addition of 10% aqueous sodium sulfite solution (15 mL), followed by water (50 mL) and K_2CO_3 (10.6 g, 1.8 equivalent) to neutralize HBr. The organic layer was separated, washed with 10% aqueous sodium sulfite and aqueous K_2CO_3 and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue co-evaporated with TBME (75 mL) to give a beige solid that was dried under vacuum overnight (13.80 g). The crude material was triturated with boiling MeOH (80 mL) for 30 min, cooled in ice and the beige solid collected by filtration. The product was dried at 60 °C under vacuum (10.53 g, 76% recovery).

EXAMPLE 13

3-Cyclopentyl-1-methyl-2-vinyl-1H-indole-6-carboxylic acid:



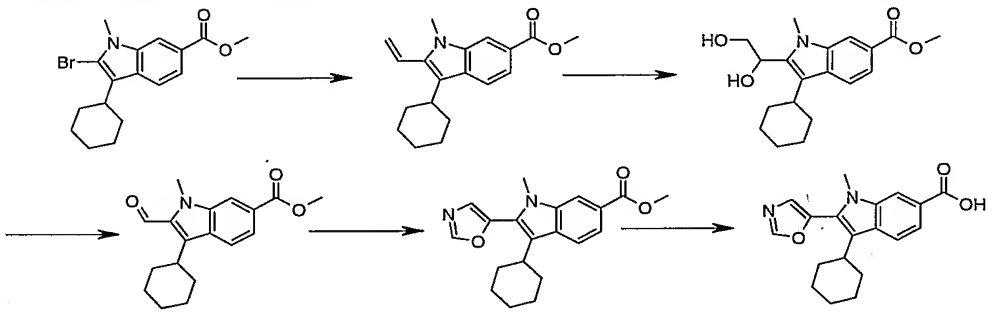
To the 2-bromoindole derivative of example 12 (2.044 g, 6.08 mmol) in dry dioxane (20 mL) was added vinyltributyltin (1.954 mL, 6.69 mmol). The solution was degassed by bubbling nitrogen for 15 min. Then bis(triphenylphosphine)

palladium (II) chloride (213.4 mg, 0.304 mmol) was added and the reaction mixture was heated at 100 °C overnight. The reaction mixture was diluted with ether and successively washed with water and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the residue was flash chromatographed (5 cm, 10% AcOEt-hexane) to afford the desired compound (1.32 g, 4.70 mmol, 77 % yield) as a white solid.

To the ester from above (153 mg, 0.54 mmol) in a mixture of THF (2.8 mL) and methanol (1.4 mL) was added an aqueous solution of lithium hydroxide (226.6 mg, 5.40 mmol in 1.6 mL of water). The reaction mixture was stirred at 50 °C for 1.5 h and diluted with water. The aqueous layer was acidified with 1M aq. HCl and extracted three times with CH_2Cl_2. The combined organic layers were successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the desired crude acid was isolated (150 mg).

EXAMPLE 14

3-Cyclohexyl-1-methyl-2-oxazol-5-yl-1H-indole-6-carboxylic acid:



To the bromide of example 4 (1.00 g, 2.855 mmol) in dry dioxane (10 mL) was added vinyltributyltin (917.8 µL, 3.141 mmol). The solution was degassed by bubbling nitrogen through for 15 min. Then bis(triphenylphosphine) palladium (II) chloride (101 mg, 0.144 mmol) was added and the solution was refluxed for 7 hrs. The reaction mixture was diluted with ether and successively washed with water and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the residue was flash chromatographed (5 cm, hexane to 2.5% AcOEt to 5% AcOEt to 10% AcOEt-hexane) to afford the desired compound (773 mg, 2.60 mmol, 91 % yield) as a pale yellow solid.

To the olefinic derivative from above (100 mg, 0.336 mmol) in a mixture of

acetone (690 µL), *tert*-butanol (690 µL) and water (690 µL) were successively added *N*-methylmorpholine *N*-oxide (NMMO; 48 mg, 0.410 mmol) and a 2.5 % solution of osmium tetroxide in *tert*-butanol (33 µL). The reaction mixture was stirred at room temperature for three days and then concentrated. The residue was dissolved in EtOAc and successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the crude diol (117 mg) was isolated.

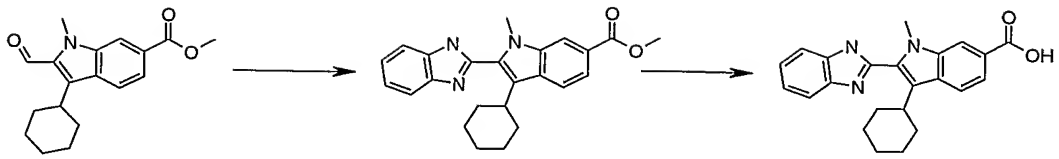
To the crude diol obtained above (*ca.* 0.336 mmol) in a mixture of THF (3.2 mL) and water (3.2 mL) at 0 °C was added sodium periodate (86.2 mg, 0.403 mmol). The cooling bath was then removed and the reaction mixture was stirred at room temperature for 1h 45 min. AcOEt was then added. The resulting solution was successively washed with 10% aq. citric acid, water, satd aq. $NaHCO_3$, water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the crude desired aldehyde was isolated (92 mg, 0.307 mmol, 91 % yield).

A mixture of the aldehyde from above (25.8 mg, 0.086 mmol), anhydrous potassium carbonate (12.4 mg, 0.090 mmol) and Tosmic (17.57 mg, 0.090 mmol) in absolute MeOH (500 µL) was refluxed for 2 h. AcOEt was then added and the mixture was successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the crude desired oxazole was isolated (28 mg, 0.083 mmol, 96 % yield).

To the ester from above (28 mg, 0.083 mmol) in a mixture of THF (425 µL), MeOH (210 µL) and water (250 µL) was added lithium hydroxide (34.8 mg, 0.830 mmol). The reaction mixture was stirred overnight at room temperature, then diluted with water and acidified with a 1N aq. HCl solution. The aqueous layer was extracted with dichloromethane (3X) and successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the title crude acid was isolated (30 mg).

EXAMPLE 15

2-(1H-Benzimidazol-2-yl)-3-cyclohexyl-1-methyl-1H-indole-6-carboxylic acid:

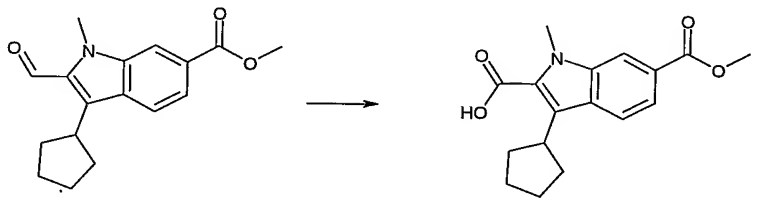


To a mixture of the aldehyde from example 14 (28 mg, 0.094 mmol) and 1,2-diaminobenzene (10.9 mg, 0.101 mmol) in acetonitrile (500 µL) and DMF (200 µL) was added chloranil (24.8 mg, 0.101 mmol). The reaction mixture was stirred at room temperature for three days. AcOEt was added and the reaction mixture was successively washed with a 1N aq. NaOH solution (2X), water (4X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the residue was flash chromatographed (1 cm, 30% AcOEt-hexane) to afford the desired benzimidazole ester derivative (11 mg, 0.028 mmol, 30 % yield).

To the ester from above (11 mg, 0.028 mmol) in a mixture of THF (240 µL), MeOH (120 µL) and water (140 µL) was added lithium hydroxide (11.7 mg, 0.280 mmol). The reaction mixture was stirred overnight at room temperature, then diluted with water and acidified with a 1N aq. HCl solution. The aqueous layer was extracted with dichloromethane (3X) and successively washed with water (2X) and brine. After the usual treatment ($MgSO_4$, filtration and concentration) the title crude acid was isolated (9 mg, 0.0241 mmol, 86 % yield).

EXAMPLE 16

3-Cyclopentyl-1-methyl-1H-indole-2,6-dicarboxylic acid 6-methyl ester:

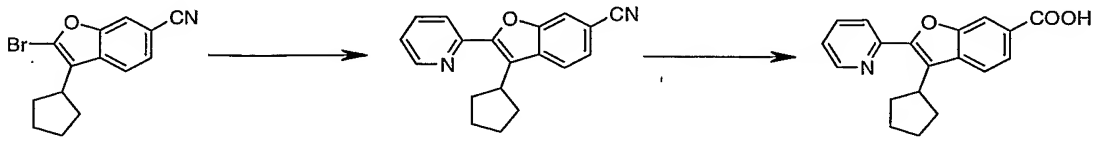


To the 3-cyclopentyl aldehyde prepared in a similar fashion to that described in example 15 (20 mg. 0.07 mmol) and 2-methyl-2-butene (541 µL, 5.11 mmol) in tert-butanol (500 µL) at 0 °C was added a freshly prepared solution of sodium chlorite (64.2 mg, 0.711 mmol) in phosphate buffer (98 mg of NaH_2PO_4 in 150 µL of water). The reaction mixture was stirred for 45 min. at room temperature then brine was added. The aqueous layer was extracted twice with EtOAc. The

combined organic layer was successively washed with a 0.5 N aq. HCl solution and brine. After the usual treatment ($MgSO_4$, filtration and concentration) 23.1 mg of the desired crude acid were isolated as a yellow solid.

EXAMPLE 18

3-Cyclopentyl-2-pyridin-2-yl-benzofuran-6-carboxylic acid:

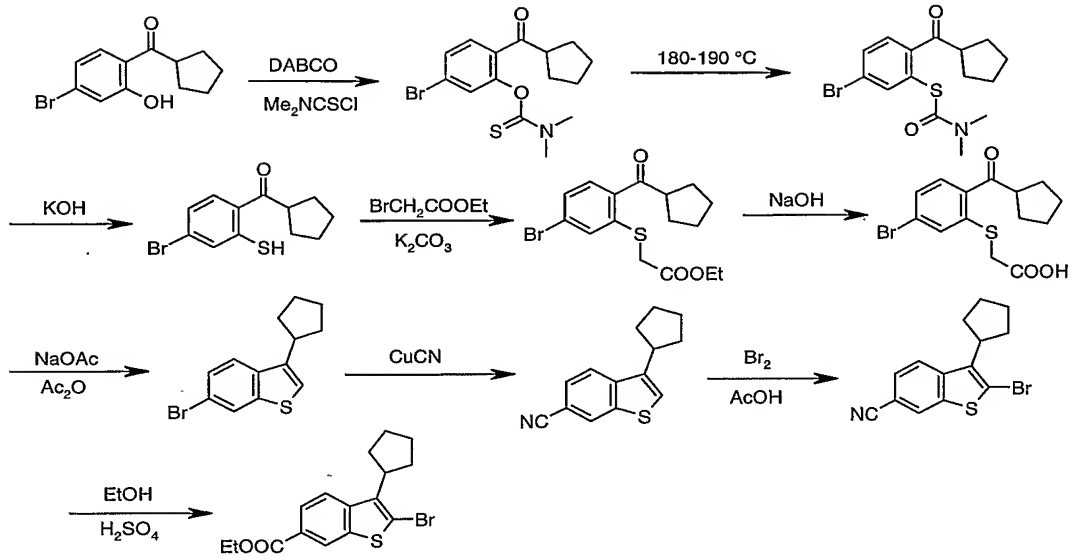


The 2-bromobenzofuran derivative of example 17 (0.850 g, 2.93 mmol), 2-tri(n-butyl)stannylpyridine (1.362 g, 3.7 mmol), triphenylphosphine (0.760 g, 2.90 mmol), lithium chloride (0.250 g, 5.9 mmol) and CuI (0.057 g, 0.3 mmol) were dissolved in DMF (30 mL) and the mixture was degassed by bubbling argon for 30 min. Tetrakis (triphenylphosphine)palladium (0.208 g, 0.18 mmol) was added and the mixture stirred at 100 °C under an argon atmosphere. After 19 h, the reaction was cooled to room temperature, poured into water (70 mL) and extracted with TBME. The organic phase was washed with water (2 X) and brine, dried ($MgSO_4$) and concentrated to give a residue that was purified by flash chromatography. The desired 2(2-pyridyl)benzofuran derivative (0.536 g, 63 % yield) was obtained as a white solid.

The nitrile from above (0.200 g, 0.694 mmol) was suspended in a mixture of conc. H_2SO_4 (5 mL), AcOH (4 mL) and water (2 mL). After refluxing for 1.5 h, TLC showed complete hydrolysis. The mixture was cooled in ice and the 10 N NaOH was added dropwise to pH 9. The aqueous layer was washed with dichloromethane and then acidified to pH 6 with 5 N HCl. The product was extracted with EtOAc, dried ($MgSO_4$) and solvents removed under reduced pressure. The desired carboxylic acid was obtained as a white solid.

EXAMPLE 19

2-Bromo-3-cyclopentyl-benzo[b]thiophene-6-carboxylic acid ethyl ester



To a solution of 3-bromo-6-cyclopentanecarbonylphenol of Example 17 (5.194 g, 19.30 mmol) in DMF (58.0 mL) was added 1,4-diazabicyclo[2.2.2]octane (4.33 g, 38.60 mmol) and dimethylthiocarbamyl chloride (4.77 g, 38.6 mmol) at room temperature. The mixture was stirred at room temperature for 3 hr. The mixture was acidified with 1 N HCl to pH 3 and then extracted with EtOAc. The organic layers were combined and washed with brine and dried over $MgSO_4$. The crude mixture was purified through a plug of silica gel with 3%EtOAc/hexanes to provide 6.976 g (100%) of the desired thiocarbamate as a colorless oil.

The neat *O*-3-bromo-6-cyclopentanecarbonyl N,N-dimethylthiocarbamate from above (43.147 g, 121.1 mmol) was heated to internal temperature of 180-190 °C for 5 hr. TLC (20% EtOAc/hexanes: R_f 0.6 (starting material), 0.5 (product)) was used to monitor the reaction progress. The crude material was used for the next reaction without further purification.

The crude *S*-3-bromo-6-cyclopentanecarbonyl *N,N*-dimethylthiocarbamate from above was dissolved in MeOH (600 mL), KOH (40.0 g, 714 mmol) was added and the mixture was heated to reflux for 1.5 h. The mixture was cooled to room temperature and the solvent was removed by rotary evaporation. The residue was dissolved in water and acidified by 6 N HCl to pH 3. It was extracted with EtOAc and the crude product was purified by a silica gel chromatography with 1-5% EtOAc/hexanes. 31.3 g (91%) of the desired thiophenol derivative was obtained as a yellow oil.

To a solution of the 3-bromo-6-cyclopentanecarbonylthiophenol from above (0.314 g, 1.105 mmol) in acetone (5.0 mL) was added K_2CO_3 (0.477 g, 3.45

mmol) followed by addition of ethyl bromoacetate (0.221 g, 0.147 mL, 1.33 mmol). The mixture was stirred overnight. The reaction mixture was filtered through filter paper and the filtrate was concentrated. Purification by silica gel with 5% EtOAc/hexanes provided 0.334 g (82%) of the product as a colorless oil.

The crude ester from above was dissolved in THF (12.0 mL), 1 N NaOH (5.0 mL) was added at room temperature. The mixture was stirred at room temperature for 2-3 hr, or until TLC indicated complete reaction. The solvent was removed by rotary evaporation. Water was added and the mixture was acidified with 6 N HCl to pH 3 and extracted with EtOAc, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was used without further purification.

To the crude acid from above was added acetic anhydride (16.0 mL), and then NaOAc (0.573 g) and the mixture was heated to reflux overnight. The mixture was cooled to room temperature and poured into a mixture of ice and toluene. 6 N NaOH was added until pH to about 7, and extracted with EtOAc, washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by silica gel with hexanes to provide 0.795 g (80%) of 6-bromo-3-cyclopentyl benzothiophene as a colorless oil.

A mixture of the 6-bromo-3-cyclopentylbenzothiophene from above (0.723 g, 2.57 mmol), and copper cyanide (0.272 g, 3.04 mmol) in DMF (1.4 mL) was heated to reflux overnight. The mixture was cooled to room temperature and diluted with EtOAc. 2 N NH_4OH was added and the mixture was stirred for 10 minutes and filtered through Celite. The aqueous layer was extracted with EtOAc. The organic layers were combined and washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was used without further purification.

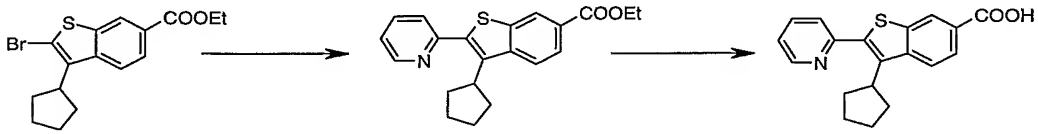
3-cyclopentyl-6-cyanobenzothiophene (17.65 g, 77.65 mmol) was dissolved in acetic acid (310 mL), bromine (49.64 g, 310.6 mmol) was added at room temperature. The mixture was stirred at room temperature overnight and HPLC was used to monitor the reaction progress. After the reaction was complete, toluene was added to the reaction mixture to remove acetic acid (3 x 100 mL). The crude product was dried under reduced pressure and used without further purification.

The crude cyano derivative from above was added to ethanol (150 mL, denatured) and conc. H_2SO_4 (45 mL) and the mixture heated to reflux for 1-2

days. After completion (HPLC) the reaction mixture was cooled to room temperature and poured into ice-water and extracted with dichloromethane (5 x 100 mL), the organic layers were combined and washed with 5% $NaHCO_3$, and brine. The solvent was removed under reduced pressure and the residue was purified with silica gel by 1% EtOAc/hexanes. The collected fractions were concentrated and the residue was slurried in methanol. The solid was filtered and washed with ice-cold methanol to provide 15.9 g (58%, two steps) of pure ethyl ester as a slight yellow solid.

EXAMPLE 20

3-Cyclopentyl-2-pyridin-2-yl-benzo[b]thiophene-6-carboxylic acid:



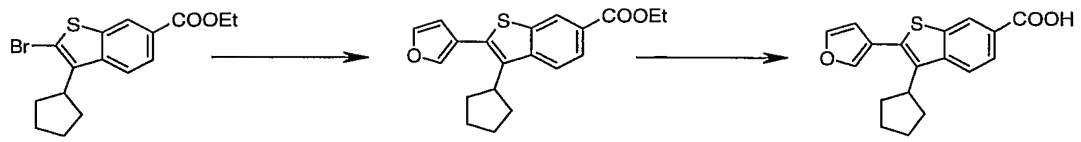
The 2-bromobenzothiophene of example 19 (0.354 g, 1.00 mmol), 2-tri(n-butyl)stannylpyridine (0.442 g, 1.2 mmol), triphenylphosphine (0.262 g, 1.00 mmol), lithium chloride (0.085 g, 2.0 mmol) and CuI (0.019 g, 0.1 mmol) were dissolved in DMF (10 mL) and the mixture was degassed by bubbling argon for 30 min. Tetrakis (triphenylphosphine)palladium (0.069 g, 0.06 mmol) was added and the mixture stirred at 100 °C under an argon atmosphere. After 24 h, the reaction was cooled to room temperature, poured into water (70 mL) and extracted with TBME. The organic phase was washed with water (2 X) and brine, dried ($MgSO_4$) and concentrated to give a residue that was purified by flash chromatography. The desired 2(2-pyridyl)benzothiophene ester (0.197 g, 56 % yield) was obtained as a pale yellow waxy solid.

The ester from above was hydrolyzed in the usual manner using NaOH, to give the title acid that could be used directly or purified by HPLC and flash chromatography.

The acid could be coupled to amine derivatives following the general procedure described in example 37.

EXAMPLE 21

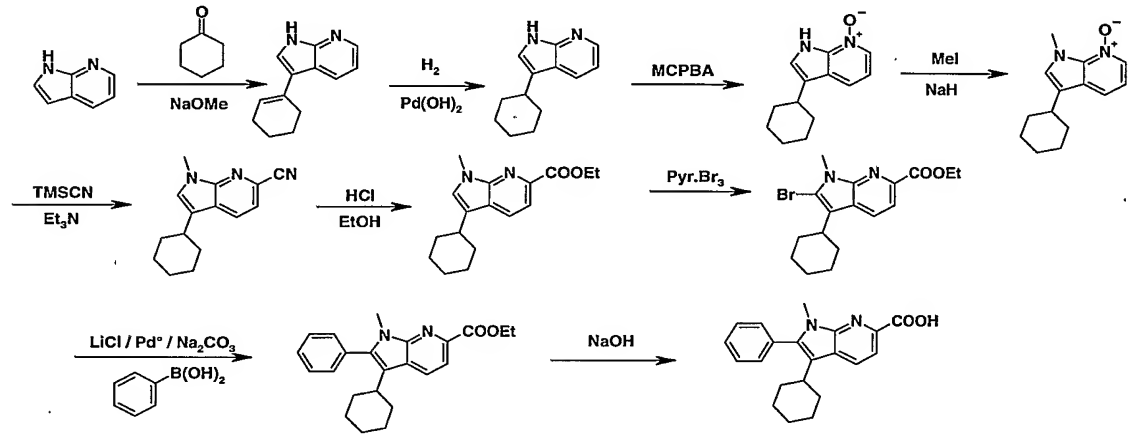
3-Cyclopentyl-2-furan-3-yl-benzo[b]thiophene-6-carboxylic acid:



The 2-bromobenzothiophene ester of example 19 was coupled to 3-furanboronic acid as described in example 3 to give the desired 2(3-furyl)benzothiophene ester in 85 % yield. Saponification of the ethyl ester was carried out with NaOH at room temperature to give the title carboxylic acid derivative.

EXAMPLE 22

3-Cyclohexyl-1-methyl-2-phenyl-1H-pyrrolo[2,3,b]pyridine-6-carboxylic acid:



7-Azaindole (15.00 g, .127 mole) was dissolved in MeOH (330 mL) and sodium methoxide (25% w/w in MeOH, 172 mL, 0.753 mole) and cyclohexanone (52.86 mL, 0.51 mole) were added. The mixture was refluxed for 60 h and then concentrated under reduced pressure. After cooling in ice-water, the reaction mixture was acidified to pH 8 with 3N HCl and the precipitated solid was collected by filtration. The product was washed with water, triturated with TBME-hexane and dried by azeotroping with toluene (19.8 g).

The material from above (15.00 g, 75.65 mmol) was dissolved in a mixture of EtOH (130 mL) and THF (30 mL) and 20% $Pd(OH)_2$ on carbon (1.30 g) was added. The mixture was hydrogenated under 1 atm of H_2 gas for 24 h, after which point additional catalyst (1.30 g) was added. After stirring under H_2 gas for an additional 16 h, the catalyst was removed by filtration and the solution evaporated under reduced pressure to give a residue that was triturated with TBME to give an amber solid (13.9 g).

The azaindole derivative from above (7.50 g, 37.45 mmol) was dissolved in DME (130 mL) and *meta*-chloroperbenzoic acid (12.943 g, 60.0 mmol) was added. After stirring for 2 h, volatiles were removed under reduced pressure and the residue suspended in water (100 mL). The mixture was basified to pH 10 by addition of saturated aqueous Na_2CO_3 solution under vigorous stirring. The solid was then collected by filtration, washed with water and a small amount of TBME, and dried (7.90 g).

The crude N-oxide from above (4.00 g, 18.49 mmol) was dissolved in DMF (350 mL) and NaH (60% dispersion, 1.52 g, 38 mmol) was added in small portions over 5 min. The mixture was stirred for 30 min and iodomethane (1.183 mL, 19 mmol) was added dropwise over 20 min to the suspension. After stirring for 3 h at room temperature, no more progress was measured by HPLC analysis. The reaction mixture was poured into water and extracted 3 times with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and evaporated to give an amber solid (3.65 g, 60% homogeneity by NMR) that was used immediately without purification.

The crude product from above (0.80 g, 3.47 mmol) was dissolved in MeCN (10 mL). Triethylamine (1.13 mL, 8.1 mmol) was added followed by trimethylsilyl cyanide (2.13 mL, 16 mmol). The solution was then refluxed for 19 h. After cooling to room temperature, the reaction was quenched by slow addition of aqueous $NaHCO_3$ and the product extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated to a residue that was purified by flash chromatography on silica gel using 15% EtOAc-hexane (0.285 g).

The nitrile (0.300 g, 1.254 mmol) was suspended in EtOH (15 mL) and hydrogen chloride gas was bubbled through for 15 min to give a clear solution. The solution was then refluxed for 1.5 h until TLC showed complete conversion of starting material. After cooling to room temperature, volatiles were removed under reduced pressure and the residue was dissolved in EtOAc. The solution was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (15-20% EtOAc-hexane) to give the desired ethyl ester as a pale yellow gum (0.227 g).

The ester from above (0.100 g, 0.35 mmol) was dissolved in THF (4 mL) and pyridinium hydrobromide perbromide (0.200 g, 0.532 mmol) was added. The mixture was stirred at 65 °C in a sealed vial for 16 h (>80% conversion). The solution was evaporated and the residue taken up into EtOAc. The solution was

washed with water and brine, dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography on silica gel (15% EtOAc-hexane). The bromide from above (0.100 g, 0.274 mmol), phenylboronic acid (0.049 g, 0.4 mmol) and lithium chloride (0.019 g, 0.45 mmol) were dissolved in a mixture of toluene (2 mL), EtOH (2 mL) and 1M Na_2CO_3 (0.43 mL). The mixture was degassed by passing argon gas through the solution for 30 min, and tetrakistriphenylphosphine palladium (0.035 g, 0.03 mmol) was added. The mixture was refluxed for 18 h after which point more catalyst (0.035 g, 0.03 mmol) was added. After refluxing for an additional 2 h, the EtOH was removed under reduced pressure. The residue was dissolved in EtOAc and the solution washed with 10% aqueous HCl and brine, and dried ($MgSO_4$). Removal of volatiles under reduced pressure gave an orange gum that was purified by flash chromatography on silica gel using 20% EtOAc-hexane (0.105 g, crude).

The partially purified ester from above (0.100 g, 0.276 mmol) was dissolved in a mixture of THF (2 mL) and EtOH (2 mL). 1N NaOH (2.8 mL) was added and the mixture stirred for 4 h at room temperature. Volatiles were removed under reduced pressure and the residue diluted with 10% aqueous HCl. The product was extracted with EtOAc (3 X), dried ($MgSO_4$), evaporated and purified by reversed-phase preparative HPLC to give the title compound.

EXAMPLE 23: INHIBITION OF NS5B RNA DEPENDENT RNA POLYMERASE ACTIVITY

The compounds of the invention were tested for inhibitory activity against the hepatitis C virus RNA dependant polymerase (NS5B), according to the following assay:

The substrates are:

a 12 nucleotide RNA oligo-uridylate (or oligo-uridine-monophosphate) (oligo-U) primer modified with biotin at the free 5'C position;

a complementary poly-adenylate (or adenosine monophospahte) (polyA) template of heterogeneous length (1000-10000 nucleotides); and

UTP-[5,6 ^{3}H].

Polymerase activity is measured as the incorporation of UMP-[5,6 ^{3}H] into the chain elongated from the oligo-U primer. The ^{3}H-labelled reaction product is captured by SPA-beads coated with streptavidin and quantified on the TopCount.

All solutions were made from DEPC treated MilliQ water [2 ml of DEPC is added

to 1 L of MilliQ water; the mixture is shaken vigorously to dissolve the DEPC, then autoclaved at 121°C for 30 minutes].

Enzyme: The full length HCV NS5B (**SEQ ID NO.1**) was purified as an N-terminal hexa-histidine fusion protein from baculovirus infected insect cells. The enzyme can be stored at –20°C in storage buffer (see below). Under these conditions, it was found to maintain activity for at least 6 months.

Substrates: The biotinylated oligo-U_{12} primer, the Poly(A) template, and the UTP-[5,6 ^{3}H] were dissolved in water. The solutions can be stored at –80°C.

Assay buffer:	20 mM Tris-HCl pH 7.5
	5 mM $MgCl_2$
	25 mM KCl
	1 mM EDTA
	1 mM DTT
NS5B storage buffer:	0.1 µM NS5B
	25 mM Tris-HCl pH 7.5
	300 mM NaCl
	5 mM DTT
	1 mM EDTA
	0.1 % n-Dodecyl maltoside
	30 % glycerol

Test compound cocktail: Just prior to assay, test compounds of the invention were dissolved in assay buffer containing 15% DMSO.

Substrate cocktail: Just prior to assay, the substrates were mixed in assay buffer to the following concentrations:

Component	Concentration in substrate cocktail	Final Concentration in assay

. RNAsin™	0.5 U/ µL	1.67 U/ µL
Biotin-oligo-U_{12} primer	3 ng/µL	1 ng/ µL
PolyA template	30 ng/ µL	10 ng/ µL
UTP-[5,6-^{3}H] 35 Ci/mmol	0.025 µCi/ µL	0.0083 µCi/ µL 0.25 µM
UTP	2.25 µM	0.75 µM

Enzyme cocktail: Just prior to assay, the RNA polymerase (NS5B) cocktail was prepared in assay buffer to the following specifications:

Component	Concentration in cocktail
Tris-HCl at **pH 7.5**	20 mM
$MgCl_2$	5 mM
KCl	25 mM
EDTA	1 mM
DTT	1 mM
n- Dodecyl maltoside	1%
NS5B	30 nM

Protocol:

The assay reaction was performed in a Microfluor™ white "U" bottom plate (Dynatech™ #7105), by successively adding:

20 µL of test compound cocktail;

20 µL of substrate cocktail; and

20 µL of enzyme cocktail

(final [NS5B] in assay = 10 nM; final [n-dodecyl maltoside] in assay = 0.33%; final DMSO in assay = 5%).

The reaction was incubated at room temperature for 1.5 hours. STOP solution (20 µL; 0.5 M EDTA, 150 ng/ µl tRNA) was added, followed by 30 µl streptavidin coated PVT beads (8mg/ml in 20 mM Tris-HCl, pH 7.5, 25 mM KCl, 0.025% NaN_3). The plate was then shaken for 30 minutes. A solution of CsCl was added (70 µL, 5 M), to bring the CsCl concentration to 1.95 M. The mixture was then allowed to stand for 1 hour. The beads were then counted on a Hewlett Packard

TopCount™ instrument using the following protocol:
Data mode: counts per minute
Scintillator: liq/plast
Energy range: low
Efficiency mode: normal
Region: 0-50
Count delay: 5 minutes
Count time: 1 minute
Expected results: 6000 cpm/well
200 cpm/well no enzyme control.

Based on the results at ten different concentrations of test compound, standard concentration-% inhibition curves were plotted and analysed to determine IC_{50}'s for the compounds of the invention. For some compounds the IC_{50} was estimated from two points.

EXAMPLE 24: SPECIFICITY OF NS5B RNA DEPENDENT RNA POLYMERASE INHIBITION

The compounds of the invention were tested for inhibitory activity against polio virus RNA dependent RNA polymerase and calf thymus DNA dependent RNA polymerase II in the format that is described for the HCV polymerase with the exception that another polymerase was used in place of the HCV NS5B polymerase.

EXAMPLE 25: CELL BASED HCV RNA REPLICATION ASSAY

Cell Culture
Huh7 cells that stably maintain a subgenomic HCV replicon were established as previously described (Lohman et al., 1999. Science **285**: 110-113) and designated as the S22.3 cell-line. S22.3 cells are maintained in Dulbecco's Modified Earle Medium (DMEM) supplemented with 10% FBS and 1mg/mL neomycin (Standard Medium). During the assay, DMEM medium supplemented with 10% FBS, containing 0.5% DMSO and lacking neomycin was used (Assay Medium). 16 hours prior to compound addition, S22.3 cells are trypsinized and diluted to 50 000 cells/ml in Standard Medium. 200µL (10 000 cells) are

distributed into each well of a 96-well plate. The plate was then incubated at 37°C with 5% $C0_2$ until the next day.

Reagents and Materials:

Product	Company	Catalog #	Storage
DMEM	Wisent Inc.	10013CV	4°C
DMSO	Sigma	D-2650	RT
Dulbecco's PBS	Gibco-BRL	14190-136	RT
Fetal Bovine Serum	Bio-Whittaker	14-901F	-20°C/4°C
Neomycin (G418)	Gibco-BRL	10131-027	-20°C/4°C
Trypsin-EDTA	Gibco-BRL	25300-054	-20°C/4°C
96-well plates	Costar	3997	RT
PVDF 0.22µm Filter Unit	Millipore	SLGV025LS	RT
Deep-Well Titer Plate Polypropylene	Beckman	267007	RT

Preparation of Test Compound

10µL of test compound (in 100% DMSO) was added to 2 ml of Assay Medium for a final DMSO concentration of 0.5% and the solution was sonicated for 15 min and filtered through a 0.22µM Millipore Filter Unit. 900µl was transfered into row A of a Polypropylene Deep-Well Titer Plate. Rows B to H, contain 400µL aliquots of Assay Medium (containing 0.5% DMSO), and are used to prepare serial dilutions (1/2) by transferring 400µl from row to row (no compound was included in row H).

Application of test compound to cells

Cell culture medium was aspirated from the 96-well plate containing the S22.3 cells. 175µL of assay medium with the appropriate dilution of test compound was transferred from each well of the compound plate to the corresponding well of the cell culture plate (row H was used as the "No inhibition control"). The cell culture plate was incubated at 37°C with 5% $C0_2$ for 72 hours.

Extraction of Total Cellular RNA

Following the 72 hour incubation period, the total cellular RNA was extracted from the S22.3 cells of the 96-well plate using the RNeasy 96 kit (Qiagen®, RNeasy

Handbook. 1999.). Briefly, assay medium was completely removed from cells and 100 µL of RLT buffer (Qiagen®) containing 143 mM β-mercaptoethanol was added to each well of the 96-well cell-culture plate. The microplate was gently shaken for 20 sec. 100 µL of 70% ethanol was then added to each microplate well, and mixed by pipetting. The lysate was removed and applied to the wells of a RNeasy 96 (Qiagen®) plate that was placed on top of a Qiagen® Square-Well Block. The RNeasy 96 plate was sealed with tape and the Square-Well Block with the RNeasy 96 plate was loaded into the holder and placed in a rotor bucket of a 4K15C centrifuge. The sample was centrifuged at 6000 rpm (~5600 x g) for 4 min at room temperature. The tape was removed from the plate and 0.8 ml of Buffer RW1 (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The RNeasy 96 plate was placed on top of another clean Square-Well Block, the tape removed and 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The tape was removed and another 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 10 min at room temperature. Tape was removed, the RNeasy 96 plate was placed on top of a rack containing 1.2-mL collection microtubes. The RNA was eluted by adding 50 µL of RNase-free water to each well, sealing plate with a new piece of tape and incubated for 1 min at room temperature. The plate was then centrifuged at 6000 rpm for 4 min at room temperature. The elution step was repeated with a second volume of 50 µl RNase-free water. The microtubes with total cellular RNA are stored at –70°C.

Quantification of Total Cellular RNA

RNA was quantified on the STORM® system (Molecular Dynamics®) using the RiboGreen® RNA Quantification Kit (Molecular Probes®). Briefly, the RiboGreen reagent was diluted 200-fold in TE (10mM Tris-HCl pH =7.5, 1mM EDTA). Generally, 50µL of reagent was diluted in 10mL TE. A Standard Curve of ribosomal RNA was diluted in TE to 2µg/mL and pre-determined amounts (100, 50, 40, 20, 10, 5, 2 and 0µL) of the ribosomal RNA solution are then transferred in a new 96-well plate (COSTAR # 3997) and the volume was completed to 100µL

with TE. Generally, column 1 of the 96-well plate was used for the standard curve and the other wells are used for the RNA samples to be quantified. 10µL of each RNA sample that was to be quantified, was transferred to the corresponding well of the 96-well plate and 90µL of TE was added. One volume (100µL) of diluted RiboGreen reagent was added to each well of the 96-well plate and incubated for 2 to 5 minutes at room temperature, protected from light (a 10 µL RNA sample in a 200 uL final volume generates a 20 X dilution). The fluorescence intensity of each well was measured on the STORM® system (Molecular Dynamics®). A standard curve was created on the basis of the known quantities of the ribosomal RNA and the resulting fluorescent intensities. The RNA concentration in the experimental samples was determined from the standard curve and corrected for the 20X dilution.

Reagents and Materials:

Product	Company	Catalog #	Storage
DEPC	Sigma	D5758	4°C
EDTA	Sigma	E5134	RT
Trizma-Base	Sigma	T8524	RT
Trizma-HCl	Sigma	T7149	RT
Collection Tube Strips	Qiagen	19562	RT
Ribogreen RNA Quantitation Kit	Molecular Probe	R11490	-20°C
Rneasy 96 Kit	Qiagen	74183	RT
Square-Well Blocks	Qiagen	19573	RT

Real-Time RT-PCR

The Real-Time RT-PCR was performed on the ABI Prism 7700 Sequence Detection System using the TaqMan EZ RT-PCR Kit from (Perkin-Elmer Applied Biosystems®). RT-PCR was optimized for the quantification of the 5' IRES of HCV RNA by using the Taqman technology (Roche Molecular Diagnostics Systems) similar to the technique previoulsy described (Martell et al., 1999. J. Clin. Microbiol. 37: 327-332). The system exploits the 5'-3' nucleolytic activity of AmpliTaq DNA polymerase. Briefly, the method utilizes a dual-labeled fluorogenic hybridization probe (PUTR Probe) that specifically anneals to the template

between the PCR primers (primers 8125 and 7028). The 5' end of the probe contains a fluorescent reporter (6-carboxyfluorescein [FAM]) and the 3' end contains a fluorescent quencher (6-carboxytetramethylrhodamine [TAMRA]). The FAM reporter's emission spectrum was suppressed by the quencher on the intact hybridization probe. Nuclease degradation of the hybridization probe releases the reporter, resulting in an increase in fluorescence emission. The ABI Prism 7700 sequence detector measures the increase in fluorescence emission continuously during the PCR amplification such that the amplified product was directly proportion to the signal. The amplification plot was analysed early in the reaction at a point that represents the logarithmic phase of product accumulation. A point representing a defined detection threshold of the increase in the fluorescent signal associated with the exponential growth of the PCR product for the sequence detector was defined as the cycle threshold (C_T). C_T values are inversely proportional to the quantity of input HCV RNA; such that under identical PCR conditions, the larger the starting concentration of HCV RNA, the lower the C_T. A standard curve was created automatically by the ABI Prism 7700 detection system by plotting the C_T against each standard dilution of known HCV RNA concentration.

Reference samples for the standard curve are included on each RT-PCR plate. HCV Replicon RNA was synthesized (by T7 transcription) *in vitro*, purified and quantified by OD_{260}. Considering that 1µg of this RNA = 2.15 X 10^{11} RNA copies, dilutions are made in order to have 10^8, 10^7, 10^6, 10^5, 10^4, 10^3 or 10^2 genomic RNA copies / 5µL. Total cellular Huh-7 RNA was also incorporated with each dilution (50ng / 5µL). 5µL of each reference standard (HCV Replicon + Huh-7 RNA) was combined with 45µL of Reagent Mix, and used in the Real-Time RT-PCR reaction.

The Real-Time RT-PCR reaction was set-up for the experimental samples that were purified on RNeasy 96 –well plates by combining 5µl of each total cellular RNA sample with 45µL of Reagent Mix.

Reagents and Materials:

Product	Company	Catalog #	Storage
TaqMan EZ RT-PCR Kit	PE Applied Biosystems	N808-0236	-20°C
MicroAmp Optical Caps	PE Applied Biosystems	N801-0935	RT
MicroAmp Optical 96-	PE Applied Biosystems	N801-0560	RT

Well Reaction Plate			

Reagent Mix preparation:

Component	Volume for one sample (µL)	Volume for One Plate (µL) (91 samples + Dead Volume)	Final conc.
Rnase-free water	16.5	1617	
5X TaqMan EZ buffer	10	980	1X
$Mn(OAc)_2$ (25mM)	6	588	3mM
dATP (10mM)	1.5	147	300µM
dCTP (10mM)	1.5	147	300µM
dGTP (10mM)	1.5	147	300µM
dUTP (20mM)	1.5	147	600µM
Forward Primer (10µM)	1	98	200nM
Reverse Primer (10µM)	1	98	200nM
PUTR probe (5µM)	2	196	200nM
rTth DNA polymerase (2.5 U/µL)	2	196	0.1 U/µL
AmpErase UNG (1U/µL)	0.5	49	0.01 U/µL
Total Volume	45	4410	

Forward Primer Sequence (SEQ ID. 2): 5' - ACG CAG AAA GCG TCT AGC CAT GGC GTT AGT - 3'

Reverse Primer Sequence (SEQ ID NO. 3): 5' - TCC CGG GGC ACT CGC AAG CAC CCT ATC AGG - 3'

Note: Those primers amplify a region of 256-nt present within the 5' untranslated region of HCV.

PUTR Probe Sequence (SEQ ID NO. 4): 6FAM - TGG TCT GCG GAA CCG GTG AGT ACA CC - TAMRA

No Template Controls (NTC): On each plate, 4 wells are used as "NTC". For these controls, 5µl of water are added to the well in place of RNA.

Thermal Cycling Conditions:

50°C	2 min	
60°C	30 min	
95°C	5 min	
95°C	15 sec	for 2 cycles
60°C	1 min	
90°C	15 sec	for 40 cycles
60°C	1 min	

Following the termination of the RT-PCR reaction the data analysis requires setting of threshold fluorescence signal for the PCR plate and a standard curve was constructed by plotting the Ct value versus RNA copy number used in each reference reaction. The Ct values obtained for the assay samples are used to interpolate an RNA copy number based on the standard curve.
Finally, the RNA copy number was normalized (based on the RiboGreen RNA quantification of the total RNA extracted from the cell culture well) and expressed as genome equivalents / µg of total RNA [ge/µg].

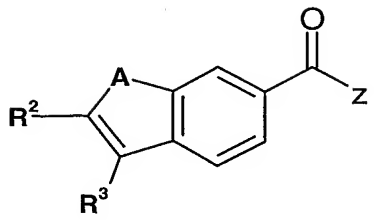
The RNA copy number [g.e./µg] from each well of the cell culture plate was a measure of the amount of replicating HCV RNA in the presence of various concentrations of inhibitor. The % inhibition was calculated with the following equation:

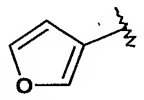
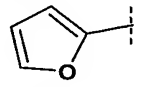
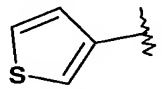
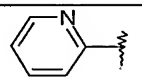
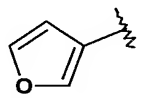
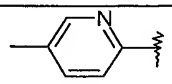
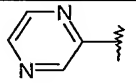
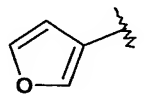
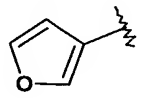
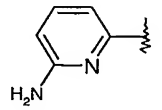
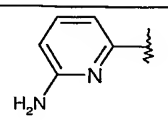
100 - [(g.e./µg inh)/(g.e./µg ctl)x 100].

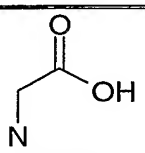
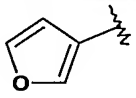
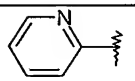
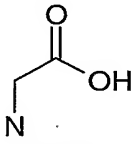
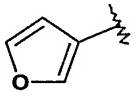
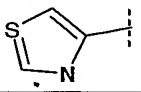
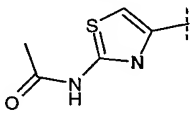
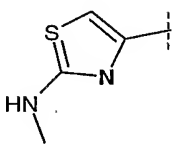
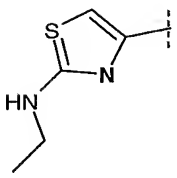
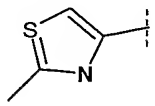
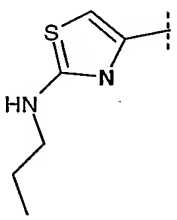
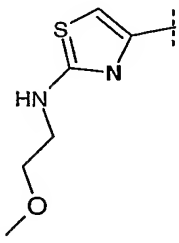
A non-linear curve fit with the Hill model was applied to the inhibition-concentration data, and the 50% effective concentration (EC_{50}) was calculated by the use of SAS software (Statistical Software System; SAS Institute, Inc. Cary, N.C.).

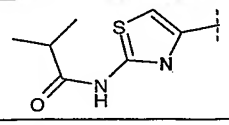
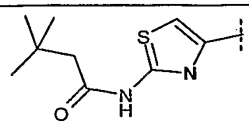
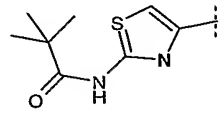
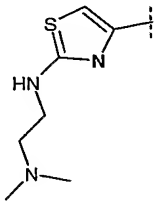
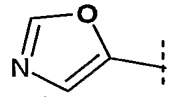
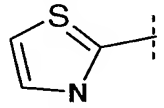
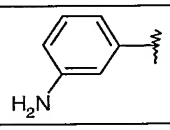
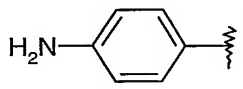
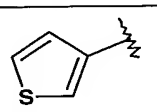
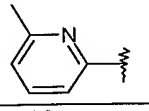
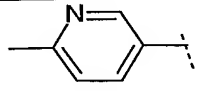
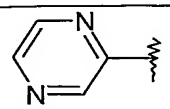
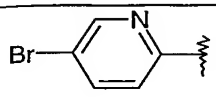
In Table 1 below, the following ranges apply:
IC_{50}: A = ≥1µM; B = 1µM-500nM; and C<500nM.
Ec_{50}: A = ≥1µM; and B = <1µM

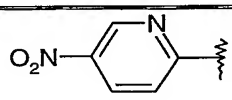
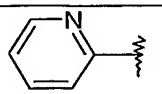
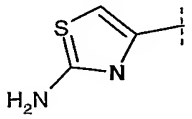
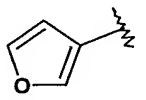
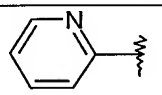
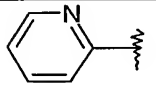
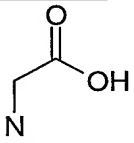
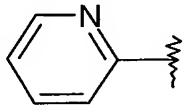
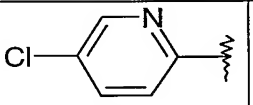
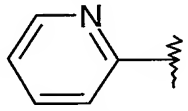
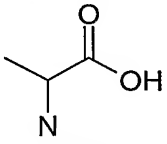
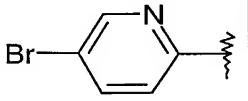
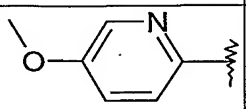
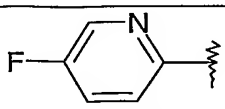
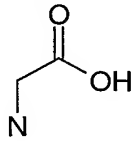
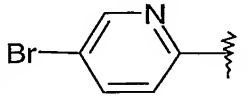
TABLE 1



Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
101	N-Me	phenyl	cyclohexyl	OH	A	--	334.1
102	NH		cyclohexyl	OH	A	A	310.0
103	NH		cyclohexyl	OH	A	--	308.0
104	NH		cyclohexyl	OH	A	--	324.0 (M-H)
105	NH	Br	cyclohexyl	OH	A	--	319.9
106	N-Me		cyclohexyl	OH	B	A	335.2
107	N-Me		cyclohexyl	OH	B	A	324.1
108	N-Me		cyclohexyl	OH	B	B	349.1
109	N-Me		cyclohexyl	OH	C	A	336.1
110	NH		cyclopentyl	OH	C	--	296.0
111	N-Me		cyclopentyl	OH	C	A	310.0
112	N-Me		cyclohexyl	OH	C	A	350.1
113	N-Me		cyclopentyl	OH	C	--	336.1

Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
114			cyclohexyl	OMe	A	A	382
115	N-Me		cyclopentyl	OH	B	A	321
116			cyclohexyl	OH	C	--	368.1
117	N-Me		cyclopentyl	OH	C	A	327.1
118	N-Me		cyclopentyl	OH	C	A	384.1
119	N-Me		cyclopentyl	OH	B	A	356.2
120	N-Me		cyclopentyl	OH	A	--	370.2
121	N-Me		cyclopentyl	OH	B	A	341.1
122	N-Me		cyclopentyl	OH	A	--	384.2
123	N-Me		cyclopentyl	OH	C	A	400.2

Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
124	N-Me		cyclopentyl	OH	A	--	384.1
125	N-Me		cyclopentyl	OH	A	--	440.2
126	N-Me		cyclopentyl	OH	A	--	426.2
127	N-Me		cyclopentyl	OH	C	A	413.2
128	N-Me		cyclopentyl	OH	C	A	311.1
129	N-Me		cyclopentyl	OH	B	A	327.1
130	N-Me		cyclopentyl	OH	A	--	335.2
131	N-Me		cyclopentyl	OH	B	A	335.2
132	N-Me		cyclopentyl	OH	C	A	326.1
133	N-Me		cyclopentyl	OH	B	A	335.2
134	N-Me		cyclopentyl	OH	B	--	335.2
135	N-Me		cyclopentyl	OH	C	A	322.2
136	N-Me		cyclopentyl	OH	B	--	399.1

Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
137	N-Me		cyclopentyl	OH	B	--	366.1
138	S		cyclopentyl	OH	A	A	324.1
139	N-Me		cyclohexyl	OH	C	--	356.1
140	S		cyclopentyl	OH	A	--	331.1
141	O		cyclopentyl	OH	A	A	308.2
142	NH		cyclohexyl	OH	A	--	321.1
143			cyclohexyl	OH	B	--	379.2
144	N-Me		cyclopentyl	OH	A	--	355.0
145	NH		cyclopentyl	OH	A	A	307.1
146			cyclohexyl	OH	A	--	471.1
147	N-Me		cyclopentyl	OH	A	--	351.1
148	N-Me		cyclopentyl	OH	B	--	339.1
149			cyclohexyl	OH	B	--	457.2

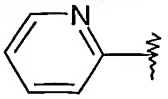
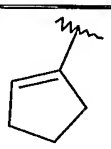
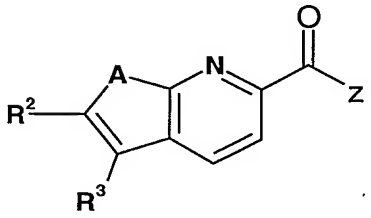
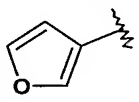
Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
150	N-Me			OH	--	--	319.0

TABLE 2

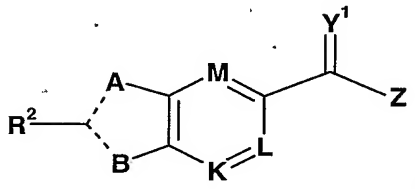


Cpd. #	A	R^2	R^3	Z	IC_{50}	EC_{50}	m/z $(M+H)^+$
201	N-Me	phenyl	cyclohexyl	OH	A	--	335.3
202	N-Me		cyclohexyl	OH	A	--	325.2

CLAIMS

WHAT IS CLAIMED IS:

1. An isomer, enantiomer, diastereoisomer, or tautomer of a compound, represented by formula I:



(I)

wherein:

A is O, S, NR^1, or CR^1, wherein R^1 is selected from the group consisting of: H, (C_{1-6})alkyl optionally substituted with:

-halogen, OR^{11}, SR^{11} or $N(R^{12})_2$, wherein R^{11} and each R^{12} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, said aryl or **Het** optionally substituted with R^{10}; or

both R^{12} are covalently bonded together and to the nitrogen to which they are both attached to form a 5, 6 or 7-membered saturated heterocycle;

----- represents either a single or a double bond;

R^2 is selected from: H, halogen, R^{21}, OR^{21}, SR^{21}, $COOR^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})_2$, $CON(R^{22})_2$, $NR^{22}C(O)R^{22}$ or $NR^{22}C(O)NR^{22}$ wherein R^{21} and each R^{22} is independently H, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, said R^{21} and R^{22} being optionally substituted with R^{20}, or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

wherein R^{10} and R^{20} is each:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{3-6})cycloalkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-$(C_{3-}$

$_{7}$)cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{150}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{150}}$;

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150}; and

wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or

- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-

(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$, or $\mathbf{R^{122}}$ is OR^{123} or $N(\mathbf{R^{124}})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

j) tetrazole, $COOR^{128}$ wherein $\mathbf{R^{128}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$; and

k) $CONR^{129}R^{130}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

wherein $\mathbf{R^{160}}$ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or

$CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,

B is NR^3 or CR^3, with the proviso that one of **A** or **B** is either CR^1 or CR^3, wherein R^3 is selected from (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**,

said alkyl, cycloalkyl, bicycloalkyl, aryl, **Het**, alkyl-aryl and alkyl-**Het** being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C_{1-6})alkyl optionally substituted with:

- OR^{31} or SR^{31} wherein R^{31} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or
- $N(R^{32})_2$ wherein each R^{32} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{32} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) OR^{33} wherein R^{33} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

c) SR^{34} wherein R^{34} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; and

d) $N(R^{35})_2$ wherein each R^{35} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{35} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

K is N or CR^4, wherein R^4 is H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^4 is OR^{41} or SR^{41}, COR^{41} or $NR^{41}COR^{41}$ wherein each R^{41}

is independently H, (C_{1-6})alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or **R**^{4} is N**R**^{42}**R**^{43} wherein **R**^{42} and **R**^{43} are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or both **R**^{42} and **R**^{43} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

L is N or C**R**^{5}, wherein **R**^{5} has the same definition as **R**^{4} defined above;

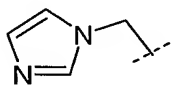
M is N or C**R**^{7}, wherein **R**^{7} has the same definition as **R**^{4} defined above;

Y^1 is O or S;

Z is O**R**^{6}, wherein **R**^{6} is H, (C_{1-6})alkyl being optionally substituted with: halo, hydroxy, carboxy, amino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, and C_{1-6} alkylamino; or **R**^{6} is C_{1-6} alkylaryl optionally substituted with: halogen, cyano, nitro, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}alkanoyl, -$(CH_2)_{1-6}$-COO**R**^{7}, -$(CH_2)_{1-6}$-CON**R**^{7}**R**^{8}, -$(CH_2)_{1-6}$-N**R**^{7}**R**^{8}, -$(CH_2)_{1-6}$-N**R**^{7}CO**R**^{8}, -$(CH_2)_{1-6}$-NHSO_2**R**^{7}, -$(CH_2)_{1-6}$-O**R**^{7}, -$(CH_2)_{1-6}$-S**R**^{7}, -$(CH_2)_{1-6}$-SO_2**R**^{7}, and -$(CH_2)_{1-6}$-SO_2N**R**^{7}**R**^{8}, wherein each **R**^{7} and each **R**^{8} is H or C_{1-6} alkyl,

or **Z** is N**R**^{9}**R**^{10} wherein each of **R**^{9} and **R**^{10} is selected from: H, C_{1-6}alkoxy, or C_{1-6}alkyl optionally substituted with halo, hydroxy, carboxy, amino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, and C_{1-6} alkylamino;

or a salt thereof;

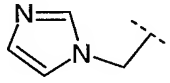
with the proviso that when **A** is C**R**^{1}, **R**^{1} is Me, **R**^{2} is pyridine or  , **B** is N**R**^{3}, **R**^{3} is Me, **K, L, M** is CH, **Y**^{1} is O, and **Z** is O**R**^{6}, then **R**^{6} is not H;

and with the proviso that when **A** is N**R**^{1}, **R**^{1} is H, **R**^{2} is phenyl, **B** is C**R**^{3}, **R**^{3} is phenyl, **K, L, M** is CH, **Y**^{1} is O, and **Z** is O**R**^{6}, then **R**^{6} is not H;

and with the proviso that when **A** is S, **R**^{2} is bromine, **B** is C**R**^{3}, **R**^{3} is Me, **K** is CH, **L** is CH, **M** is C**R**^{7}, **R**^{7} is H or Me, **Y**^{1} is O, and **Z** is O**R**^{6}, then **R**^{6} is not H;

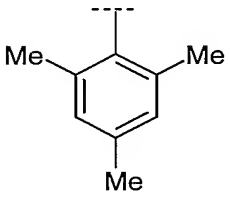
and with the proviso that when **A** is O, R^2 is H, **B** is CR^3, R^3 is phenyl, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not H;

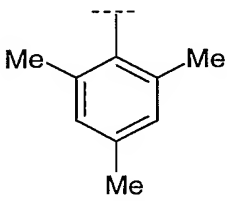
and with the proviso that when **A** is CR^1, R^1 is Me, R^2 is pyridine, **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Me;

and with the further proviso that when **A** is CR^1, R^1 is Me, R^2 is  , **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Et;

and with the further proviso that when **A** is CR^1, R^1 is CH, R^2 is Me, **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Et;

and with the further proviso that when **A** is CR^1, R^1 is Et, R^2 is Me, **B** is NR^3, R^3 is Me, **K, L, M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not $CH_2CH_2N(Me)_2$;

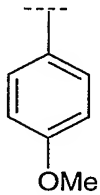
and with the further proviso that when **A** is CH, R^2 is Me, **B** is NR^3, R^3 is  , **K** is N, **L** is CR^5, R^5 is Me, **M** is CR^7, R^7 is OH, Y^1 is O, and **Z** is OR^6 then R^6 is not Et;

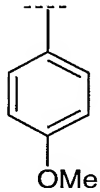
and with the further proviso that when **A** is NR^1, R^1 is Me, R^2 is Br, **B** is CR^3, R^3 is  , **K** is N, **L** is CR^5, R^5 is Me, **M** is CR^7, R^7 is Br, Y^1 is O, and **Z** is OR^6, then R^6 is not Me;

and with the further proviso that when **A** is NR^1, R^1 is H, R^2 is Cl, **B** is CR^3, R^3 is Et,

K is CH, **L** is CH, **M** is CH, Y^1 is O, **Z** is OR^6, then R^6 is not Me;

and with the further proviso that when **A** is NR^1, R^1 is H, R^2 is phenyl, **B** is CR^3, R^3 is phenyl, **K** is CH, **L** is CH, **M** is CR^7, R^7 is Me, Y^1 is O, **Z** is OR^6, then R^6 is not Et;

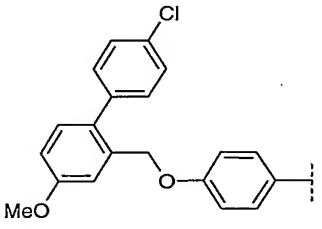
and with the further proviso that when **A** is NR^1, R^1 is H, R^2 is 

, **B** is CR^3, R^3 is 

, **K** is CH, **L** is N, **M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Et;

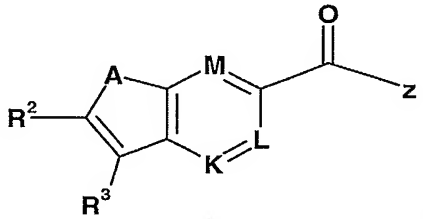
with the further proviso that when **A** is S, R^2 is Br, **B** is CR^3, R^3 is Me, **K** is CH, **L** is CH, **M** is CH, Y^1 is O, and **Z** is OR^6, then R^6 is not Me;

and with the further proviso that, when **A** is NR^1, R^1 is H, R^2 is:



, **B** is NR^3, R^3 is cyclohexyl, **K, L, M** is CH, Y^1 is O, **Z** is OR^6, then R^6 is not H.

2. The compound according to claim 1, having the following formula (II):

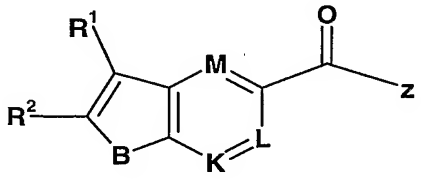


(II)

wherein, preferably, **A** is O, S, or NR^1.

3. The compound according to claim 2, wherein **A** is NR^1.

4. The compound according to claim 1, wherein having the following formula (III):



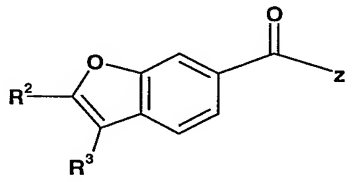
(III)

wherein, preferably, **B** is NR^3.

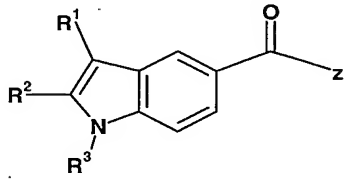
5. The compound according to claim 1, wherein **M, K** and **L** is CH or N.

6. The compound according to claim 5, wherein **M, K** and **L** is CH.

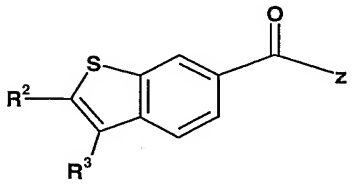
7. The compound according to claim 1, having the following formulae:



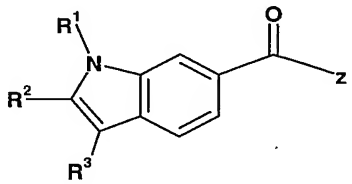
IIa ,



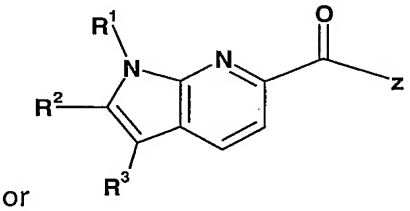
IIIa



IIb ,



IIc



or

IId

wherein R^1, R^2, R^3 and **Z** are as defined in claim 1.

8. The compound according to claim 1, wherein R^1 is selected from the group consisting of: H or (C_{1-6})alkyl.

9. The compound according to claim 8, wherein R^1 is H, CH_3, isopropyl, or isobutyl.

10. The compound according to claim 9, wherein R^1 is H or CH_3.

11. The compound according to claim 10, wherein R^1 is CH_3.

12. The compound according to claim 1, wherein R^2 is selected from: H, halogen, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**; wherein (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, aryl or **Het** is optionally substituted with R^{20}, wherein R^{20} is defined as:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is preferably:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het** and heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, or (C_{3-7})cycloalkyl, and R^{112} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, $(C_{1-}$

$_6$)alkyl or (C_{3-7})cycloalkyl, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, and heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160}, or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

13. The compound according to claim 12, wherein R^2 is selected from: aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, N_3, or

a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}$

alkyl);

b) (C_{1-6})alkoxy;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; being optionally substituted with halogen or:

- OR^{161} or $N(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle;

f) $NHCOR^{117}$ wherein R^{117} is (C_{1-6})alkyl, $O(C_{1-6})$alkyl or $O(C_{3-7})$cycloalkyl;

i) CO-aryl; and

k) $CONH_2$, $CONH(C_{1-6}alkyl)$, $CON(C_{1-6}alkyl)_2$, CONH-aryl, or $CONHC_{1-6}$alkyl-aryl.

14. The compound according to claim 13, wherein R^2 is aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, or

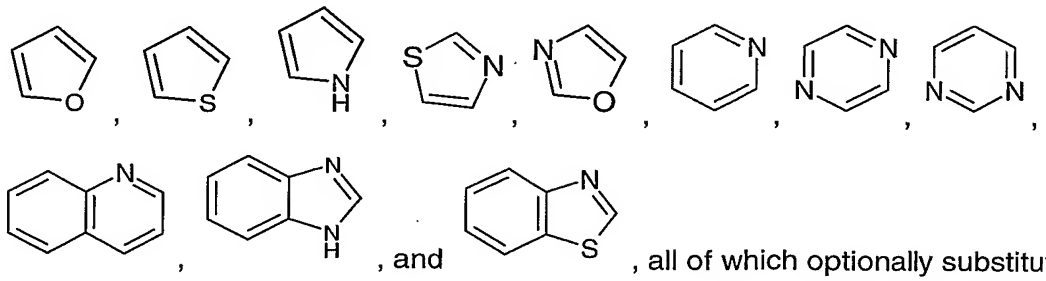
a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}alkyl)$;

b) (C_{1-6})alkoxy; and

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; or being optionally substituted with halogen or:

- OR^{161} or $N(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle.

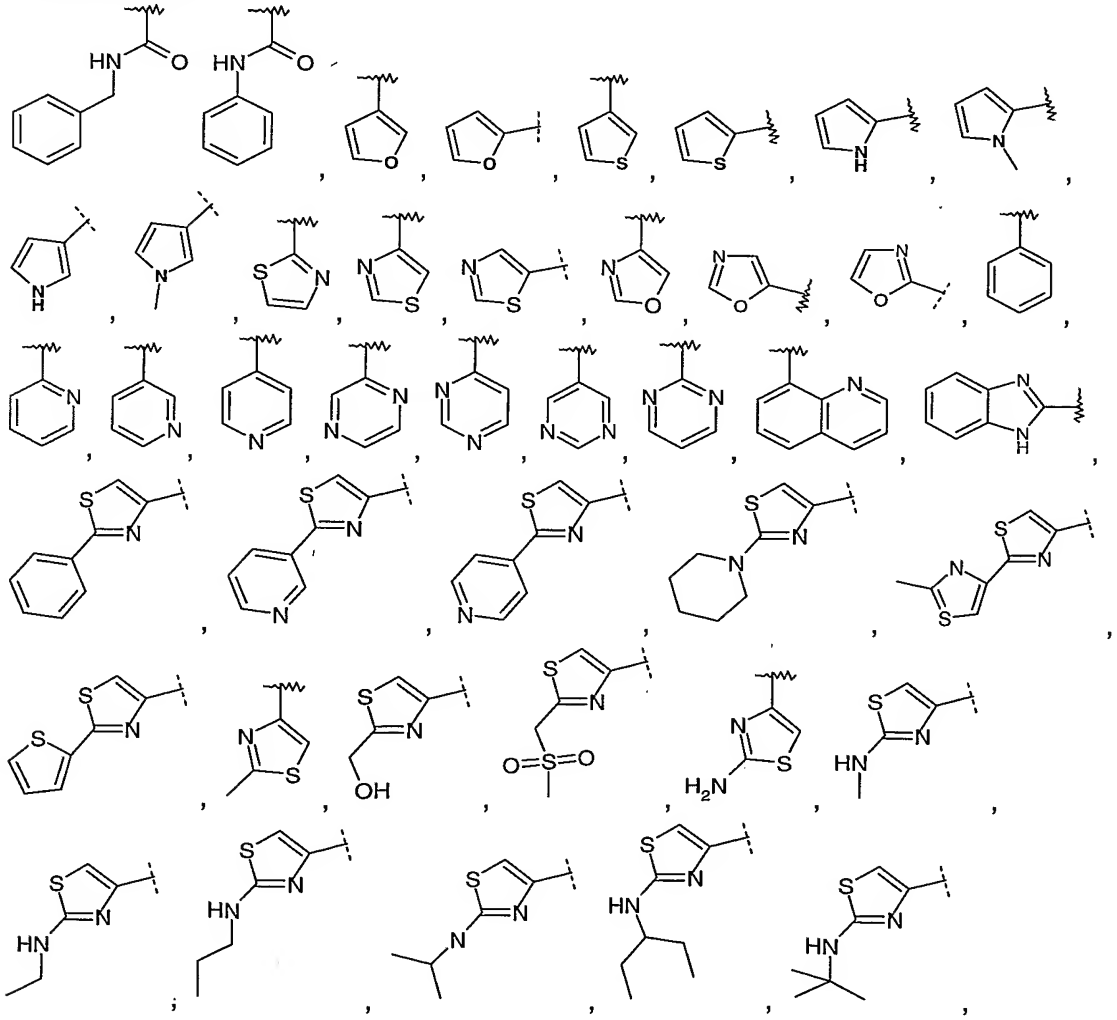
15. The compound according to claim 14, wherein R^2 is phenyl or a heterocycle selected from:

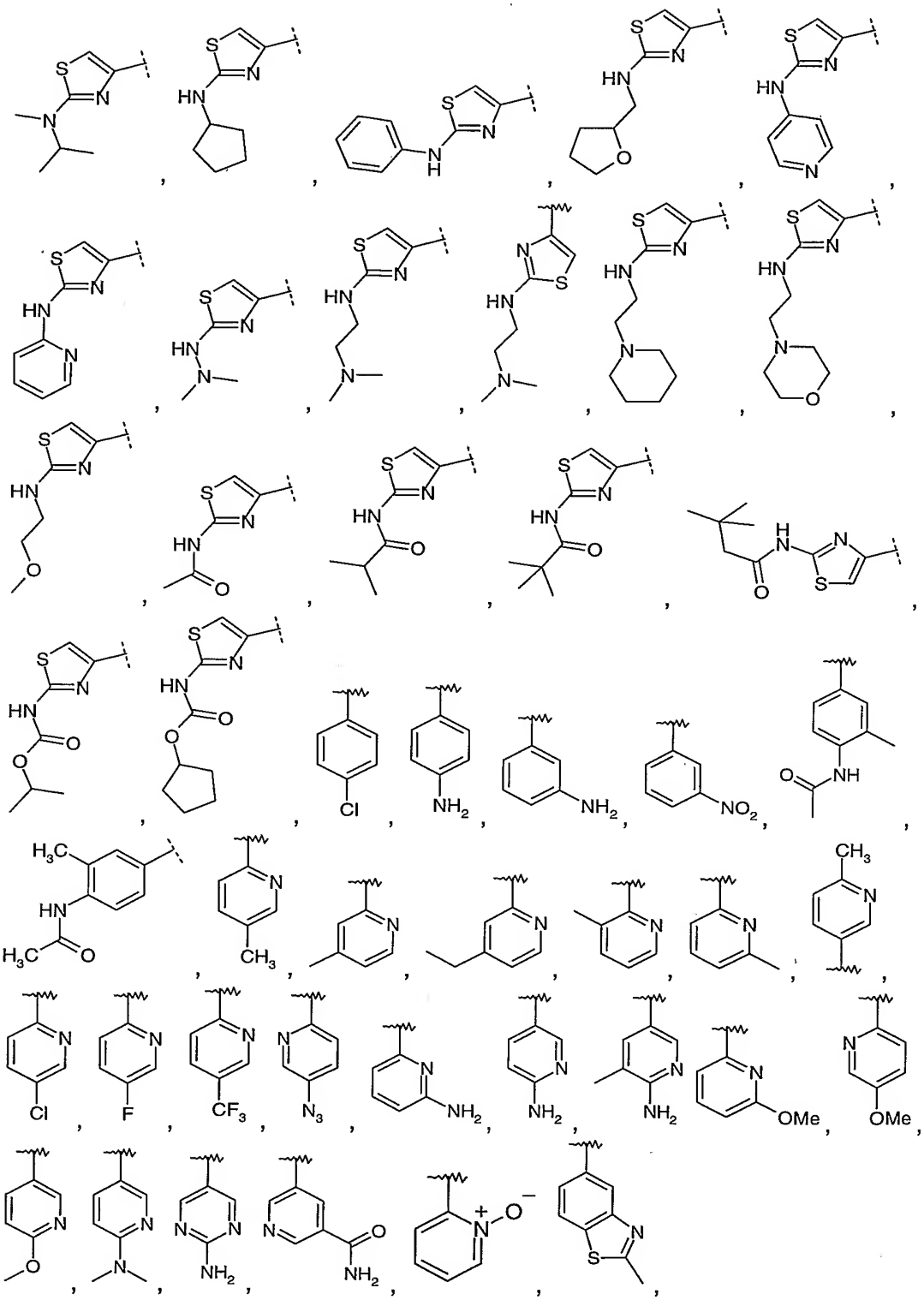


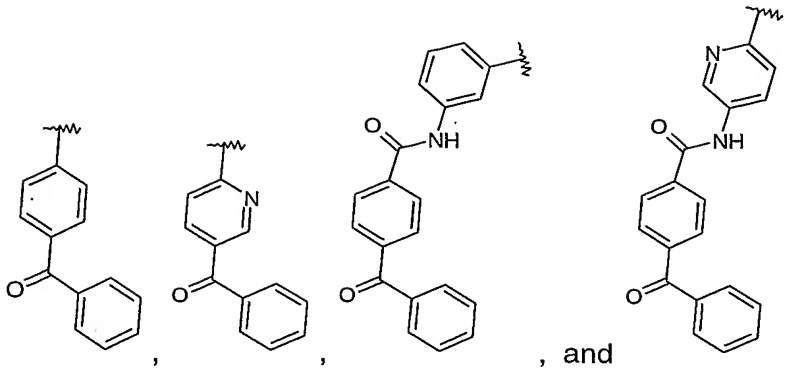
, and , all of which optionally substituted as defined in claim 14.

16. The compound according to claim 15, wherein R^2 is selected from:

H, Br, $CH=CH_2$,

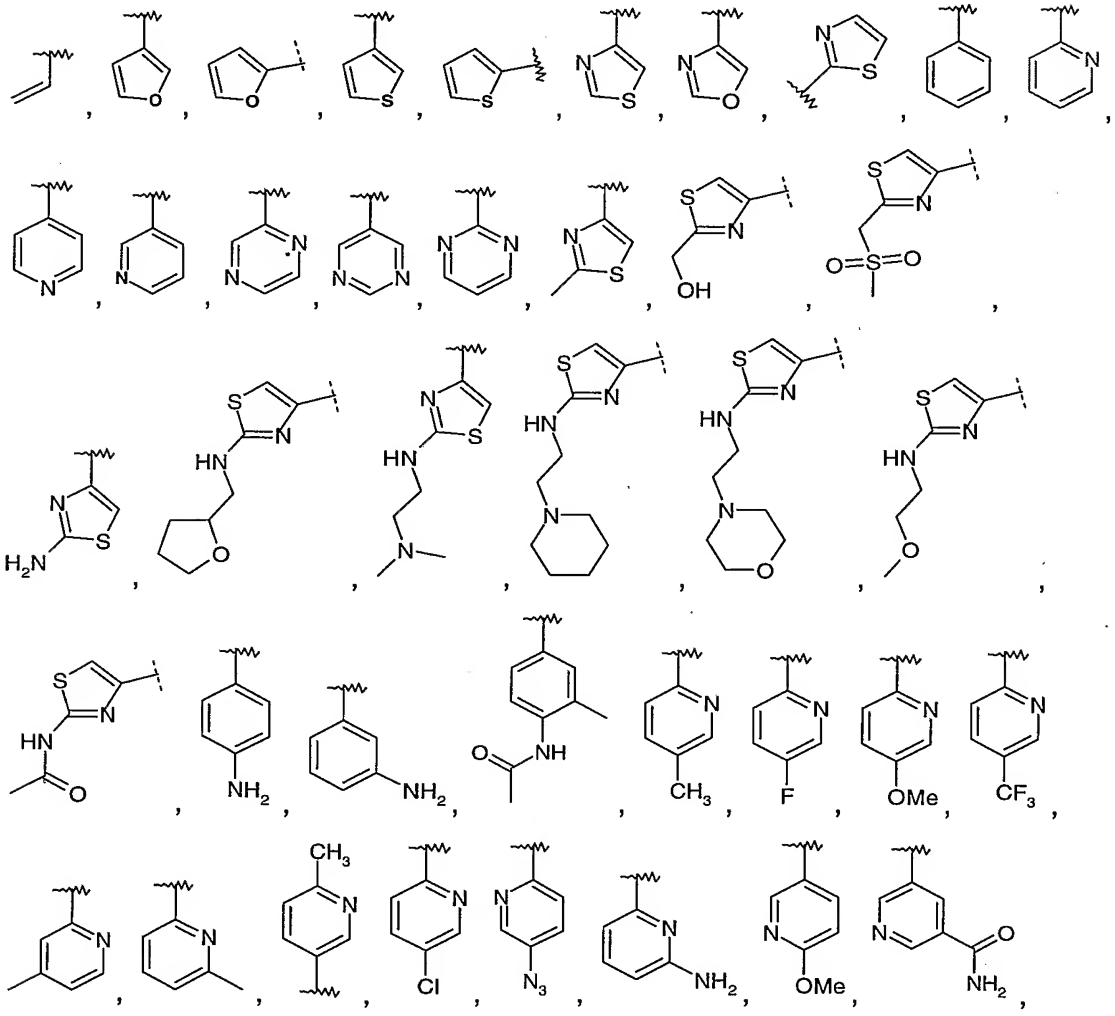


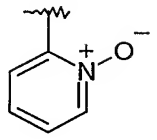




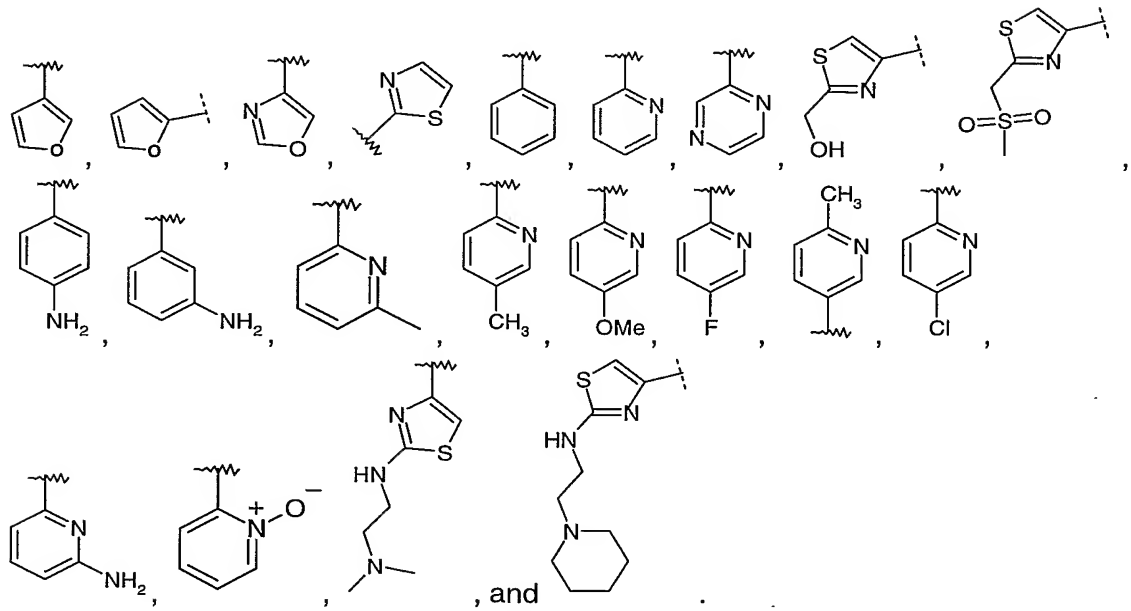
, , , and .

17. The compound according to claim 16, wherein R^2 is selected from:



and  .

18. The compound according to claim 17, wherein R^2 is selected from:



19. The compound according to claim 1, wherein R^3 is selected from (C_{3-7})cycloalkyl, (C_{3-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, or **Het**.

20. The compound according to claim 19, wherein R^3 is (C_{3-7})cycloalkyl.

21. The compound according to claim 20, wherein R^3 is cyclopentyl, or cyclohexyl.

22. The compound according to claim 1, wherein Y^1 is O.

23. The compound according to claim 1, wherein **Z** is OR^6, wherein R^6 is H, (C_{1-6})alkyl being optionally substituted with: halo, hydroxy, carboxy, amino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, and C_{1-6} alkylamino; or R^6 is C_{1-6} alkylaryl optionally substituted with: halogen, cyano, nitro, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}alkanoyl, $-(CH_2)_{1-}$

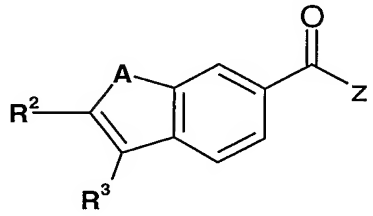
$_{6}$-COOR^{7}, -(CH$_2$)$_{1-6}$-CONR^{7}R^{8}, -(CH$_2$)$_{1-6}$-NR^{7}R^{8}, -(CH$_2$)$_{1-6}$-NR^{7}COR^{8}, -(CH$_2$)$_{1-6}$-NHSO$_2$R^{7}, -(CH$_2$)$_{1-6}$-OR^{7}, -(CH$_2$)$_{1-6}$-SR^{7}, -(CH$_2$)$_{1-6}$-SO$_2$R^{7}, and -(CH$_2$)$_{1-6}$-SO$_2$NR^{7}R^{8}, wherein each **R**^{7} and each **R**^{8} is H or C$_{1-6}$ alkyl,

or **Z** is NR^{9}R^{10} wherein each of **R**^{9} and **R**^{10} is selected from: H, C$_{1-6}$alkoxy, or C$_{1-6}$alkyl optionally substituted with halo, hydroxy, carboxy, amino, C$_{1-6}$ alkoxy, C$_{1-6}$alkoxycarbonyl, and C$_{1-6}$ alkylamino.

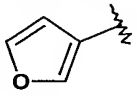
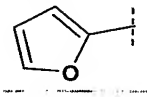
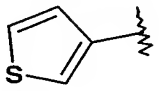
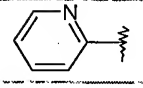
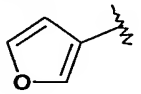
24. The compound according to claim 23, wherein **Z** is OH or O(C$_{1-6}$alkyl) or **Z** is NR^{9}R^{10} wherein **R**^{9} is H and **R**^{10} is H or C$_{1-6}$alkyl.

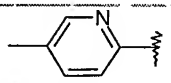
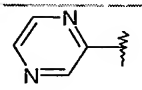
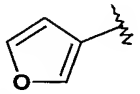
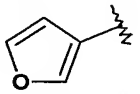
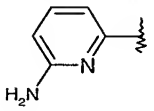
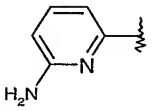
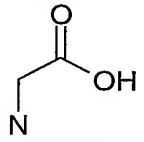
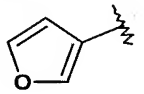
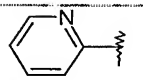
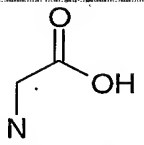
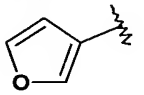
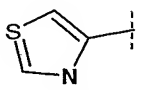
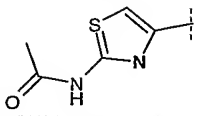
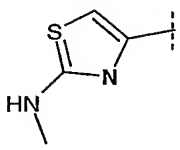
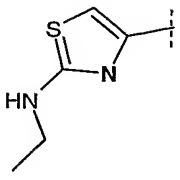
25. The compound according to claim 24, wherein **Z** is OH.

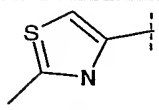
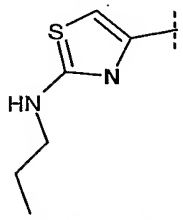
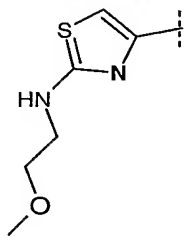
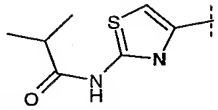
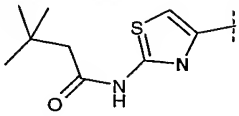
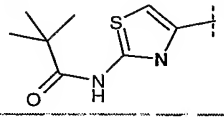
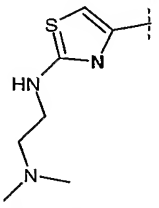
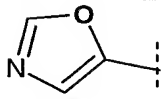
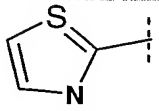
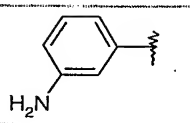
26. A compound selected from compounds of formula:

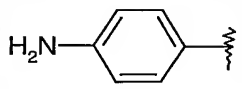
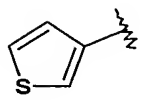
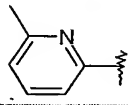
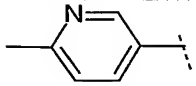
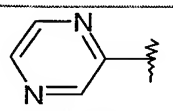
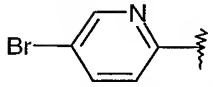
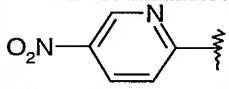
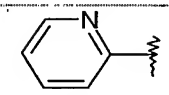
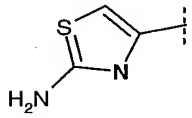
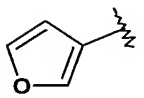
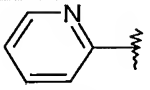
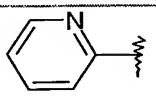
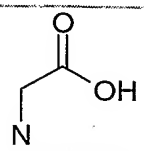
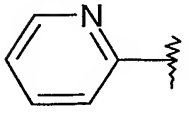
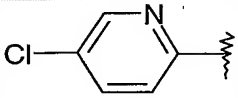


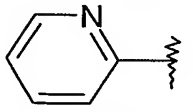
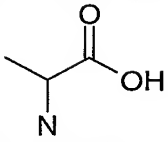
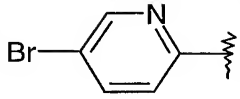
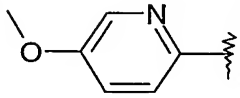
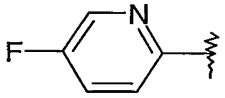
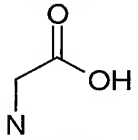
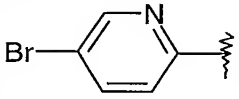
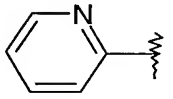
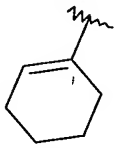
wherein **A**, **R**^{2}, **R**^{3} and **Z** are as defined below:

Cpd. #	A	R^{2}	R^{3}	Z	
101	N-Me	phenyl	cyclohexyl	OH	;
102	NH		cyclohexyl	OH	;
103	NH		cyclohexyl	OH	;
104	NH		cyclohexyl	OH	;
105	NH	Br	cyclohexyl	OH	;
106	N-Me		cyclohexyl	OH	;
107	N-Me		cyclohexyl	OH	;

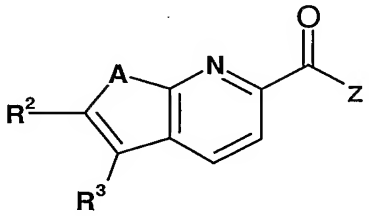
Cpd. #	A	R^2	R^3	Z	
108	N-Me		cyclohexyl	OH	;
109	N-Me		cyclohexyl	OH	;
110	NH		cyclopentyl	OH	;
111	N-Me		cyclopentyl	OH	;
112	N-Me		cyclohexyl	OH	;
113	N-Me		cyclopentyl	OH	;
114			cyclohexyl	OMe	;
115	N-Me		cyclopentyl	OH	;
116			cyclohexyl	OH	;
117	N-Me		cyclopentyl	OH	;
118	N-Me		cyclopentyl	OH	;
119	N-Me		cyclopentyl	OH	;
120	N-Me		cyclopentyl	OH	;

Cpd. #	A	R^2	R^3	Z	
121	N-Me		cyclopentyl	OH	;
122	N-Me		cyclopentyl	OH	;
123	N-Me		cyclopentyl	OH	;
124	N-Me		cyclopentyl	OH	;
125	N-Me		cyclopentyl	OH	;
126	N-Me		cyclopentyl	OH	;
127	N-Me		cyclopentyl	OH	;
128	N-Me		cyclopentyl	OH	;
129	N-Me		cyclopentyl	OH	;
130	N-Me		cyclopentyl	OH	;

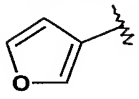
Cpd. #	A	R^2	R^3	Z	
131	N-Me		cyclopentyl	OH	;
132	N-Me		cyclopentyl	OH	;
133	N-Me		cyclopentyl	OH	;
134	N-Me		cyclopentyl	OH	;
135	N-Me		cyclopentyl	OH	;
136	N-Me		cyclopentyl	OH	;
137	N-Me		cyclopentyl	OH	;
138	S		cyclopentyl	OH	;
139	N-Me		cyclohexyl	OH	;
140	S		cyclopentyl	OH	;
141	O		cyclopentyl	OH	;
142	NH		cyclohexyl	OH	;
143			cyclohexyl	OH	;
144	N-Me		cyclopentyl	OH	;

Cpd. #	A	R^2	R^3	Z	
145	NH		cyclopentyl	OH	;
146			cyclohexyl	OH	;
147	N-Me		cyclopentyl	OH	;
148	N-Me		cyclopentyl	OH	;
149			cyclohexyl	OH	; and
150	N-Me			OH	.

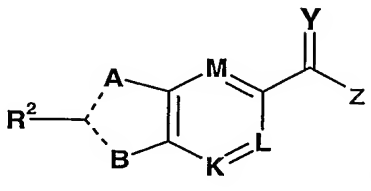
27. A compound selected from compounds of formula:



wherein **A**, R^2, R^3 and **Z** are as defined below:

Cpd. #	A	R^2	R^3	Z	
201	N-Me	phenyl	cyclohexyl	OH	; and
202	N-Me		cyclohexyl	OH	.

28. A compound represented by Formula Ia:



(Ia)

wherein:

A is O, S, NR^1, or CR^1;

B is NR^3 or CR^3;

R^1 is selected from the group consisting of: H, (C_{1-6})alkyl, benzyl, $(C_{1-6}$ alkyl)-$(C_{6-10}$aryl), $(C_{1-6}$ alkyl)-5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, and 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said benzyl and said heteroatom are optionally substituted with from 1 to 4 substituents selected from the group consisting of: COOH, $COO(C_{1-6}$ alkyl), halogen, and $(C_{1-6}$ alkyl);

R^2 is selected from the group consisting of: H, halogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, pyridine-N-oxide , and 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S,

said phenyl, heterocycle and heterobicycle being optionally substituted with from 1 to 4 substituents selected from the group consisting of: halogen, $C(halogen)_3$, (C_{1-6})alkyl, OH, $O(C_{1-6}$ alkyl), NH_2, and $N(C_{1-6}$ alkyl$)_2$;

R^3 is selected from the group consisting of: 5-, 6- or 7-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, norbornane, (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-$(C_{1-6}$ alkyl);

M is N, CR^4, or COR^5, wherein R^4 is selected from the group consisting of: H, halogen, and $(C_{1-6}$ alkyl); and R^5 is selected from the group consisting of: H and $(C_{1-6}$ alkyl);

K and **L** is N or CH;

----- represents either a single or a double bond;

Y is O;

Z is OR^6 or NR^6R^{6a}, wherein R^6 is selected from the group consisting of: H, (C_{1-6})alkyl, wherein said alkyl is optionally substituted with from 1 to 4 substituents selected from: OH, COOH, $COO(C_{1-6})$alkyl, (C_{1-6})alkyl, said alkyl being optionally substituted with from 1 to 4 substituents selected from: COOH, $NHCO(C_{1-6}$ alkyl), NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$;

or a salt thereof.

29. A compound of the formula I according to claim 1, or a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

30. A pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition according to claim 30, further comprising immunomodulatory agent.

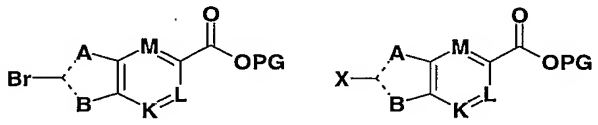
32. The pharmaceutical composition according to claim 31, wherein said immunomodulatory agent is selected from: α-, β-, δ- γ-, and ω-interferons.

33. The pharmaceutical composition according to claim 30, further comprising ribavirin or amantadine.

34. The pharmaceutical composition according to claim 30, further comprising another inhibitor of HCV polymerase.

35. The pharmaceutical composition according to claim 34, further comprising an inhibitor of other HCV target, selected from: helicase, polymerase, metalloprotease and IRES.

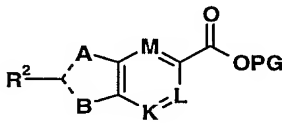
36. An intermediate of formula (1a) or (1b):



1a or 1b

wherein **A, B, K, L**, and **M** are as defined in claim 1, **PG** is H or a carboxy protecting group and **X** is a metal.

37. A process for producing compounds of formula (iii):

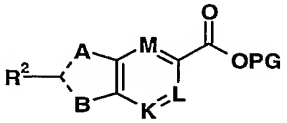


(iii)

wherein **A**, R^2, **B**, **K**, **L**, **M, PG** and **X** are as defined in claim 36, comprising:

a) coupling, in the presence of a metal catalyst, a base and an additive in an appropriate solvent, intermediate (1a) according to claim 36, with R^2-**X**.

38. A process for producing compounds of formula (iii),



(iii)

wherein **A**, R^2, **B**, **K**, **L**, **M,** and **PG** are as defined in claim 36, comprising:

a) coupling, in the presence of a metal catalyst, a base and an additive in an appropriate solvent, intermediate (1b) according to claim 36, with R^2-**X'**, wherein **X'** is as defined in claim 36.

39. A process according to claim 37 or 38, wherein said metal catalyst is selected from: Pd, Ni, Ru and Cu.

40. A process according to claim 37 or 38, wherein said additive is selected from: phosphine ligand, Cu salt, Li salt, ammonium salt and CsF.

41. A process according to claim 37 or 38, wherein said metal is selected from: Li, $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, $B(OH)_2$, $B(OC_{1-6}alkyl)_2$ and metal halide.

42. Use of a compound of formula I according to claim 1, for the manufacture of a medicament for the treatment of HCV infection.

SEQUENCE LISTING

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Asn Met Val Tyr Ser Thr Thr Ser Arg Ser Ala Ala Leu Arg Gln Lys
65                  70                  75                  80
Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp
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Val Leu Lys Glu Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu
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Leu Ser Val Glu Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Lys
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Lys Leu Gln Asp Cys Thr Met Leu Val Asn Gly Asp Asp Leu Val Val
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Ile Cys Glu Ser Ala Gly Thr Gln Glu Asp Ala Ala Asn Leu Arg Val
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Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Leu Pro
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Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val
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Ser Val Ala His Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg
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Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His
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Thr Pro Ile Asn Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr
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Leu Trp Ala Arg Met Val Leu Met Thr His Phe Phe Ser Ile Leu Leu
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